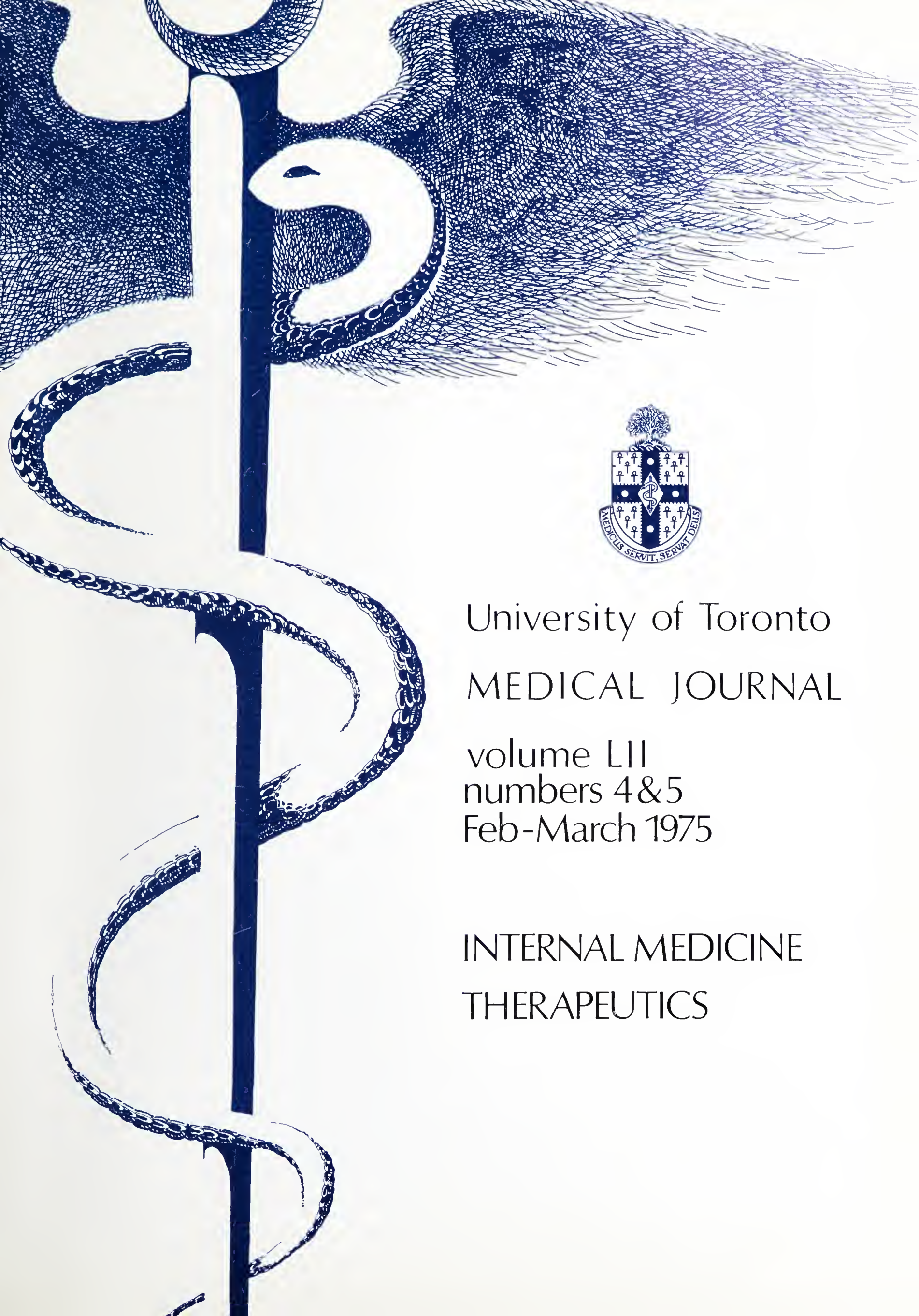

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Guest Editorial

CHARLES HOLLENBERG attended the University of Manitoba where he received his B.Sc. and M.D. degrees. He graduated in 1955 and was awarded the University of Manitoba gold medal in medicine. Between 1955 and 1960 he was Resident in Medicine at the Montreal General Hospital and the New England Center Hospital, Boston. He then joined the Department of Medicine at McGill University and became Professor of Medicine there in 1969. In 1670 Dr. Hollenberg became Professor and Chairman of the Department of Medicine at the University of Toronto, and Physician-in-Chief at the Toronto General Hospital.

Internal Medicine

While there are many reasons why medical students are among the most fortunate members of our society, one of the most important is the multitude of career choices available to them upon graduation. These careers are so varied in nature that they can fit almost any personality type and life style objective. The purpose of this editorial is to indicate to medical students at the University of Toronto what the field of Internal Medicine encompasses and what characteristics go into the making of a fine Internist.

The recent explosion of new scientific knowledge in Medicine has led to the development of increasing specialization. As a result of this development, the field of Internal Medicine now consists of a host of inter-related disciplines. These include Cardiology, Respirology, Endocrinology, Nephrology, Immunology, Oncology, Infectious Disease, Dermatology, Neurology, Haematology, Rheumatology and Clinical Pharmacology. The individual who chooses a career in Internal Medicine has the option of practising in the general field of Internal Medicine and caring for patients with a wide variety of illnesses or of becoming subspecialized and confining all clinical activities to one of the special branches of Internal Medicine. Some Internists combine both approaches and while remaining competent in the broad area of Internal Medicine, develop a special interest in one of the subspecialties and thus divide their time between practice in the more general and in the specialized areas. In Canada, and particularly in Ontario, there is a trend towards the centralization of pure subspecialists within university teaching hospitals and within a few large community hospitals. Most community hospitals, however, are staffed with Internists who have an interest in the broad field of Internal Medicine, some of whom may also have particular expertise in a particular branch of this specialty.

At present, the Royal College regulations for certification in Internal Medicine require that an individual have four years of postgraduate training, one of which can be a straight medical internship. For those preparing for a career in General Internal Medicine, three of these years must be in a general field of Internal Medicine (one year of the three can be a straight internship) while one year can be spent in research, in a special branch of Internal Medicine or in a related discipline, such as Pathology. Thus, a postgraduate trainee who wishes to qualify in General Internal Medicine, but who wishes to have a special interest in one area, will spend three years in a general medical program and one year in the area of his particular interest. For those preparing for pure subspecialty practice, the Royal College requires two core years of Internal Medicine followed by two years in the subspecialty of choice. There are some individuals who wish to be certified both in General Internal Medicine and in a subspecialty

and these individuals are required to have five postgraduate years, of which three are in General Internal Medicine and two are in the subspecialty of choice. The Department of Medicine at the University of Toronto has postgraduate training programs in General Internal Medicine and in all subspecialty disciplines.

Medical students are always, and very rightly, concerned about the opportunities for practice which are available upon completion of their postgraduate studies. While this is a complex and constantly changing problem, there are certain definite trends that are evident now throughout Canada and in Ontario. There is a substantial continuing need for General Internists and in particular for General Internists who have special knowledge in a particular branch of Internal Medicine and yet remain capable of functioning in the broad field of Internal Medicine. This need is most acute in community hospitals. In these institutions the General Internist functions primarily as a consultant to family doctors and to other specialists. In addition, the Internist is involved in acute care work in intensive care areas. Finally, and very importantly, the community Internist provides continuing care to a large number of patients with chronic serious illnesses, such as diabetes, hypertension, chronic chest disease, etc. In some areas in Canada, the General Internist continues to provide primary care, that is, care to patients who have not been seen previously by other physicians. While this particular kind of care is coming increasingly under the purview of the family doctor, there remain areas in this country in which, because of limited medical manpower, the Internist must perform this function in addition to all of his other activities.

In addition to a continuing and significant need for General Internists, there are at present some subspecialty areas which are under-staffed, both in Ontario and in Canada. These areas include Cardiology, Gastroenterology, Rheumatology, Dermatology, Oncology, Infectious Disease and Respirology. Practice opportunities for individuals with subspecialty training in these areas are available not only in the university teaching hospitals, but also in the larger community hospitals.

With this background, it is possible to outline with some precision the characteristics which are required in an individual planning a career in Internal Medicine or one of its specialties. These characteristics include, and in no special order, intelligence, a facility for meeting with people and for enjoyment of inter-personal relationships, an orderly and questioning mind, an ability to read rapidly and retain information, and an interest, if not an aptitude, for those scientific disciplines which underlie the specialty of Internal Medicine. It is also important to remember that the Internist, because of his consultative role, works very closely with the family doctor and with a variety of other specialists. Thus, he must have the kind of personality which lends itself to collaborative and cooperaitve patient management. It is the ability to lead a life in which both humanistic and scientific proclivities can be brought out which makes a career in Internal Medicine so attractive to so many.

If you are the kind of medical student who enjoys working with people, who gets pleasure out of the in depth analysis of problems, who assimilates new knowledge with some facility and who has an interest and, hopefully, an aptitude in medical science, then there is a career waiting for you in Internal Medicine. The opportunities are numerous and the professional satisfactions immense.

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Magnetics in Medicine

Murray Treloar, B.Sc., 7T5

"Magnetism is a peculiarly hidden subject, in the sense that it is all around us, part of our daily lives, and yet most people are unaware or have forgotten that their lives would be utterly different without magnetism. There would be no electric power as we know it, no electric motors, no radio and no T.V. If electricity and magnetism are sister sciences, then magnetism is surely the poor relation."

B. D. Cullity (Ref. 1)

INTRODUCTION

Centuries before Christ it was known that a certain metal, plentiful in the state of Magnesia*, would attract iron. This metal came to be named magnetite, after its country of origin. During the middle ages, a bar of magnetite was made to float by placing it on wood and the resulting device was used as a compass for sea navigation. From this usage arose the alternate name "lodestone", Old English for "waystone".

In 1820 Han Christian Oersted, a Danish physicist, observed that in the neighbourhood of a current-carrying conductor, effects were produced similar to those near a permanent magnet; forces acted on other magnets, on pieces of iron and on other current-carrying conductors.

These phenomena are thought of now in terms of the magnetic field: the special forces in space produced by a current. The magnetic properties of some materials can be considered to be the result of particular currents within the materials; each crystal of iron, for example, in a sense contains a large net circulating current made up of aligned electrons spinning about their own axes[2].

The unit of magnetic force is the Oersted (Oe). Typical values are 10^{-5} Oe in interplanetary space, 0.5 Oe at the surface of the earth (geomagnetism), 1000 Oe at the surface of an Alnico magnet and 300,000 Oe at the surface of one of the largest electromagnets available.

CLINICAL APPLICATIONS OF MAGNETISM

1. Investigative Uses

Magnetocardiography. As we have seen, electrical currents are associated with magnetic fields. The same ion currents from the heart and brain that produce the electrocardiogram and electroencephalogram also produce a magnetic field outside the body. The magnetic field of the heart was first detected by Baule and McFee[3, 4] and subsequent investigators have confirmed their results [2, 5, 6, 7]. If we consider the electrical activity in the heart as if arising from a dipole[6] (a clump of positive charges separated by a finite distance from an equal clump of negative charges), the right hand rule† gives the direction of the magnetic field of the heart (Fig. 1). The current will flow from the positive side of the dipole layer through the conducting tissues of the body and back to the negative dipole layer. This current flow produces a magnetic flux which leaves the chest from the right side of the heart, circles around in front of the chest, and returns back into the chest on the left side of the heart. The record of this magnetic flux, the magnetocardiogram (MCG), is similar to the usual ECG since both arise from the ion currents of the heart (Fig. 2).

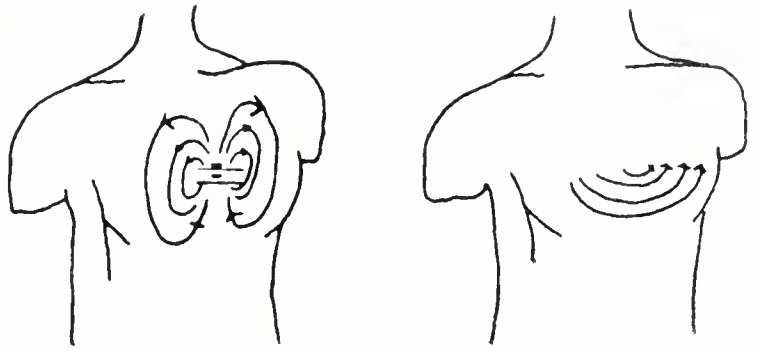


FIG. 1 – Simple electrical model showing the heart producing a magnetic field outside the torso. The normal heart is a dipole "battery" producing ion currents in the torso conductor; these produce magnetic field lines outside and perpendicular to the torso.

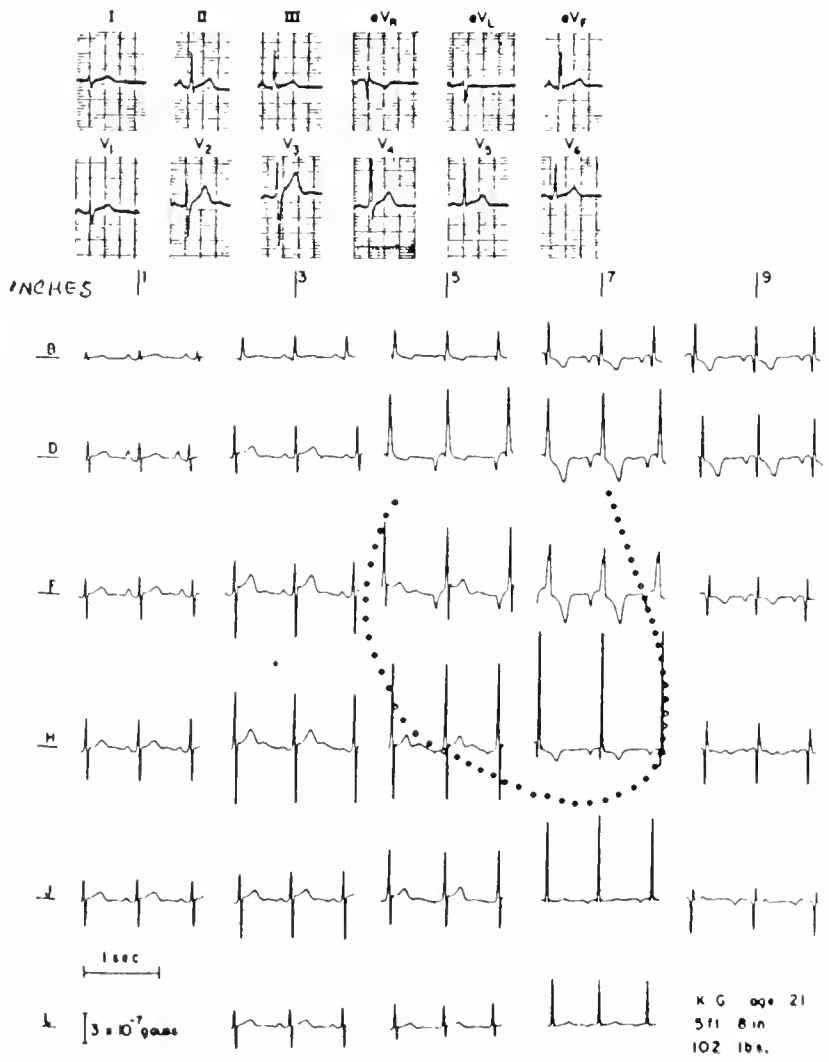


FIG. 2 – Magnetocardiogram from a normal male subject, as well as the standard 12-lead electrocardiogram. This magnetocardiogram is only of the component of the magnetic vector which is perpendicular to the chest. The outline of the heart was taken from the chest x-ray. (Reference 6)

The advantages of magnetocardiography are firstly, that a record similar to the normal ECG can be made with no electrodes attached to the subject and no need

* Corresponds roughly to modern Turkey.

† If the fingers of your right hand point in the direction of current flow, your thumb will extend in the direction of the associated magnetic field.

for the subject to disrobe. It is conceivable that the total time required to take such a record will be well under one minute, thus possibly providing a means for obtaining records at a cost which makes mass screening possible. A second advantage of the magnetocardiogram is that certain events which are invisible to the ECG could be recorded by the MCW*. One such event is the current of injury thought to arise from infarcted myocardium, and said to produce the S-T segment shift of the ECG in infarction. Using the MCG it has been shown experimentally in dogs that steady currents of injury do indeed accompany infarction, but are not related to the S-T segment shift[3]. It is possible that magnetic detection of currents of injury will lead to a new tool for detecting damaged internal tissue, not only from heart but from other organs as well.

The MCG is not yet in clinical use because expensive shielding and computerized monitoring equipment are required to detect the heart's magnetic field (10^{-5} Oe) over the ambient geomagnetic field (10^{-1} Oe). Efforts are being made to overcome this difficulty.

Magnetoencephalography. In a manner analogous to magnetocardiography, one may record a fluctuating magnetic field around the human head; the field is produced by the alpha-rhythm currents commonly seen on the electroencephalogram (EEG)[8]. The magnetoencephalogram (MEG) resembles the EEG and may also provide additional information about the electrical activity of the brain in the same way that the MCG complements the ECG.

Magnetorheography. Faraday's Law states that when a conductor moves through a magnetic field, a current tends to flow in the conductor in a direction perpendicular to both the magnetic field and the direction of motion. The physiologist would like to measure blood flow without disturbing the flow, vessel or physiology of the animal, and Faraday's Law provides a means of achieving this goal. When a body is placed in a high magnetic field, the blood flow-induced current (electromotive force) can be detected with a surface electrode[9].

There are many other methods of measuring limb blood flow – ultrasound, dye-dilution and plethysmography are a few examples – and it is too early in the development of these various techniques to evaluate their relative usefulness.

2. Therapeutic Uses

Inhibition of Tumor Growth. The results of several experiments, reviewed by D'Souza[10], indicate that the use of magnetic fields to control tumor growth may be possible. The experiment of Weber and Cerilli[11] is an example in this regard. Mammary adenocarcinoma mouse tumor cells were exposed to a large magnetic field for 20 minutes and subsequently injected into carrier-strain mice. Mice receiving tumor cells exposed to the magnetic field had a mean survival of 18 days; the mean control survival was 9 days. In addition, another group of mice with a small mammary adenocarcinoma tumor in the hind leg was exposed to the same magnetic field strength in the region of the tumor for 20 minutes with a resulting mean survival of 18 days, compared to a mean survival of 7 days in controls. There has not been to my knowledge any report in the English literature on the use of a magnetic field in human cancer therapy.

Foreign Bodies. The removal of ferromagnetic intraocular foreign bodies by means of a magnet is a well-established procedure in ophthalmology[12]. A few reports have appeared on the use of magnets for foreign body removal from other locations, such as the gastrointestinal tract and the trachea[13, 14].

Intracranial Aneurysms. Cerebral aneurysms are associated with a 45% mortality from subarachnoid hemorrhage. Surgical attempts at cure that require visual exposure of the aneurysm are frequently unsuccessful because of the problems of brain retraction and manipulation. These two factors have led to the development of an alternate method of treatment. A small burr hole is made and under stereotactic control a magnet-tipped central lumen probe is placed in contact with the aneurysm. Iron particles are injected through the probe and retained in the aneurysm by the magnet-tip. The iron particles promote thrombus formation in the aneurym; the probe is removed after about one week and the resultant metallic thrombus permanently obliterates the pouch (Fig. 3)[15, 16].

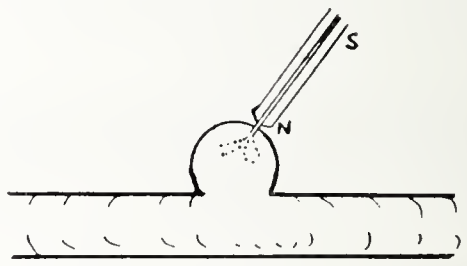


FIG. 3 – Occlusion of an aneurysm. See text for narrative.

One of the originators of this technique, Alksne, reported in 1966[15] on his experimental and clinical experience with the probe. He found the probe "inexpensive, easy to use and effective". He continues, "Moreover, because the probe is inserted through a small burr hole, the operation can be performed under local anesthesia. Consequently, it may be possible to institute stereotactic surgery immediately after the patient is admitted to hospital and thereby remove the risk of recurrent hemorrhage which accompanies the prevailing practice of delayed treatment".

Drug-Homing. Japanese investigators[17] have recently suggested that magnetically-labelled drugs could be localized to given body sites by means of an external magnetic field. This manoeuvre would be particularly valuable in cancer chemotherapy. For example, in the management of malignant disease metastatic to the liver, an established technique in chemotherapy is selective perfusion of this organ by cannulation of the portal vein. By comparison, magnetic direction of chemo-

* For example, consider both voltage and magnetic measurements on a spherical surface in space. Within this spherical surface let there exist a ring of current concentric with the sphere. There will be zero potential difference between any two surface points, yielding no internal information, while magnetic measurements will reveal a circular source distribution.

therapeutic agents would offer the advantages of (1) delivery of the drug through an arm vein, and (2) treatment of metastases in body sites other than the liver which are without the unique blood supply of this organ. By current methods this requires arterial cannulation.

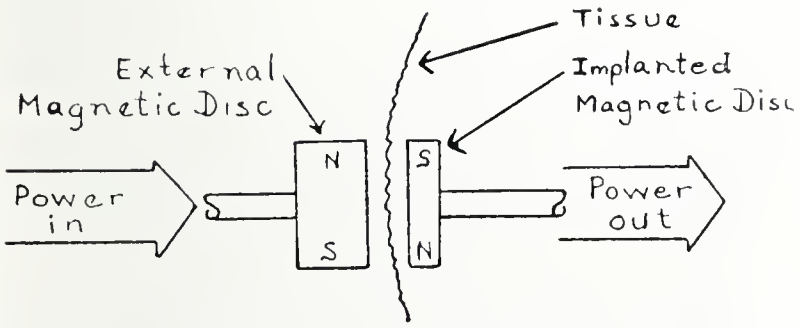


FIG. 4 – Coupled magnets to drive body implants.

Driving Body Implants. An externally-placed rotating magnet can be used to drive an internal device (Fig. 4)[18]. This mechanism has been used in CSF pumps to control hydrocephalus and is under investigation for use in powering an artificial heart. Compared to battery-powered systems, the power source here is external and renewable without surgery.

BASIC SCIENCES APPLICATIONS OF MAGNETISM

Basic scientists are like children. Given a puddle, they prefer to walk through it, because they have never before been through that puddle, rather than find a way around it in order to stay dry (which is applied research). Having traversed the puddle, they can describe its effects – the soggy sock and the squeaky shoe – and explain to mother-granting-agency that the trip was made because, in doing so, they might have stumbled on a Dinky toy concealed in the puddle's depths. The Dinky toy part of the explanation is necessary, although highly theoretical, for it provides a good reason to traverse the next puddle that arises; mother may even believe it, a little.

All biological and physical events on earth occur in a geomagnetic field of about 500 mOe. Basic scientists thought it would be interesting to study these events in extremely high and low (zero) magnetic fields. Some interesting effects were observed[10, 11, 22-28] and some of the explanations for these effects are the subject of the following paragraphs.

Barnothy has pointed out that magnetic fields provide a unique means of probing biological systems[19]. Biological processes are mainly complex chemical reactions. Chemical properties of molecules result from the interactions of the magnetic and electric fields of the particles – electrons and nuclei – making up the molecules. Consequently, electric and magnetic fields would seem to be the natural experimental devices for obtaining information about how biological systems go about their business. However, electric fields turn out to be unsuitable. The medium in which the chemical reactions of biological systems occur is an electrolyte and as such a conductor of electricity; this makes it difficult to "hit" reacting molecules, since an applied field is conducted around the target by the surrounding medium. This restriction does not apply to magnetic fields because the medium is essentially non-magnetizable. Thus the magnetic field hits the target and seems ideally suited as a probe of biological systems.

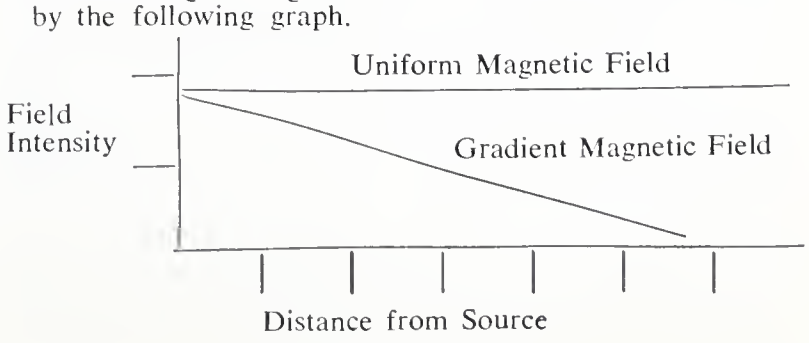
This explanation has one large difficulty: when a field is shot at, say, a cellular enzyme and its substrate in a test tube, nothing seems to happen. This is because the energy which a magnetic field can impart to a biological system is minuscule compared to the energy of thermal motion at room temperature. To circumvent this difficulty an amplification mechanism must be interposed between the basic effect of the field and the observed phenomenon. An example of this amplification principle is the exposure of embryos to a magnetic field. At the time of exposure, no change is apparent in the embryo. However, during the course of further growth and differentiation, an initially invisible change becomes obvious as altered morphology or function. This then explains why most observations are made in *in vivo* experiments where a built-in amplification mechanism exists.

Current thinking about what happens before the amplification divides changes into membrane-, enzyme- and DNA-based events. At the membrane level it has been suggested that a gradient field* creates shear forces which will disrupt the cell membrane[20]. Tumor cells have weak cell membranes so that this principle might be of use in cancer therapy. Another suggestion is that gradient fields induce lateral ionic drifts, thus altering ion distribution within the cell membrane[11]. Membrane transport of ions and molecules might also be changed, the argument here being that rod-like protein-cholesterol molecules align in an applied field such that their properties are markedly changed [21].

Enzyme reaction rates might be altered. In this instance one would expect iron-containing enzymes to be particularly sensitive. One effect is an inhibition of cellular respiration[25]. This could well result from interaction of iron in the cytochrome system with the magnetic field.

DNA as a site of magnetic action is suggested by the sensitivity of embryonic, tumor and hematopoietic cells to magnetic fields[10, 11, 23-25, 28]. These cells are all rapidly dividing and therefore sites of DNA synthesis. Because the effect, in the majority of cases, is one of decreased growth rather than production of mutants, it has been suggested that there is an inhibition of DNA replication rather than a destruction of DNA molecules. Theoretical arguments have been advanced to support this reasoning[11].

* The meaning of a "gradient" vs a "uniform" field is shown by the following graph.



These basic science pursuits have been dubbed "biomagnetism": the science of processes and functions in living organisms induced by static magnetic fields[19]. The puddle has been waded through once, the soggy-sock effect described and explanations of why puddle-wading is an activity likely to bring results have been forthcoming. However, the number of papers appearing since 1970 in this area is fewer than between 1965 and 1970. This state of affairs is unfortunate in a field that seems to be on the verge of exciting discoveries, some of which may find applications in the palliation of cancer.

Electron paramagnetic resonance and nuclear magnetic resonance are two spectroscopic techniques employing magnetic fields These are well established and of great value in *observing* molecular species. They are mentioned here for the sake of completeness.

CONCLUDING REMARKS

Magnets make marvelous gadgets, and
Magnetology may replace cardiology.
Tumors now hear vicious rumours that
Magnetic rays will end their days.
Electric eels have magnetic fields, so
Magnetism lost may be evolution's cost.

ACKNOWLEDGEMENT

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Histoplasmosis: A Review of Clinical Presentations and Management

Michael J. Howcroft, 7T6

INTRODUCTION

Histoplasmosis is an important fungal disease endemic to many regions of North America including southern Ontario and Quebec. The infection is asymptomatic in the majority of cases and only rarely fatal (only 3 deaths due to histoplasmosis were reported in Ontario during the period from 1962 to 1973[1]); yet it is important for its protean clinical manifestations which often closely resemble tuberculosis.

BACKGROUND

Histoplasmosis is the disease state resulting from infection with the organism *Histoplasma capsulatum*, a dimorphic fungus of the class "Fungus Imperfecti" (no sexual state) and a member of the family "Moniliaceae" (deep mycoses).

It was first discovered as a pathogen in the Panama Canal zone in 1905 by Samuel T. Darling[2], who falsely identified it as an animal parasite. It was established as a fungus disease by Henrique da Rocha Lima in 1912[3], and in 1932 DeMonbreun[4] cultured the organism, describing its morphology and growth characteristics in detail.

The work of Christie and Peterson[5], and Palmer[6] in the mid 1940's showed that histoplasmosis was a common disease, and more prevalent in certain geographical areas. Previous to this time histoplasmosis was thought to be rare and uniformly fatal.

EPIDEMIOLOGY AND PREVALENCE

All the available evidence points to the existence of a saprophytic reservoir of the fungus in soil and organic debris (particularly chicken feces and bat guano), from which both men and animals, when exposed and susceptible, are infected.

Studies of histoplasmin skin sensitivity and case prevalence show that the disease is found world wide[7]. In North America, endemic areas are concentrated in the eastern and central United States and in Canada along the St. Lawrence and Ottawa river valleys. Epidemics have been known to occur in areas removed from these sites of predilection, raising the possibility that other etiologic factors may be involved.

In Ontario, studies[8, 9] have shown skin sensitivity to be common in the southeastern province along the St. Lawrence and Ottawa river valleys, and endemic in areas of southwestern Ontario. In a sample population of 400 from the St. Thomas area, there was up to a 79% incidence of positive skin reactions to histoplasmin. Other investigators[10, 11] have demonstrated that Montreal is an area of endemicity.

PATHOGENESIS

H. capsulatum grows in the mycelial phase in soil and excreta, and this is the direct source of all infections. Macroconidia (Fig. 1b) are inhaled and cause an acute inflammatory response similar to tuberculosis which, depending on the innoculum and host factors, results in sub-clinical or symptomatic infection. Once in the lungs, the spores develop into the delicate parasitic yeast phase of the organism (Fig. 1c).

The yeast cells are engulfed by macrophages and other cells of the reticuloendothelial system and undergo intracellular multiplication. This leads to diffuse lesions and nodular accumulations of epithelioid and giant cells of the Langhan's type. In both the diffuse lesions and typical granuloma, caseous necrosis may be seen (Fig. 1a). The necrotic areas become encapsulated and then go on to subsequent calcification. The primary pulmonary lesion, like that of tuberculosis, consists of parenchymal and regional lymph node foci.

FIG. 1a: Shown is the edge of a necrotic lymph node surrounded by fibrous tissue and adjacent granulomatous inflammatory reaction. The normal architecture of the lymph node has been destroyed. (Hematoxylin and Eosin X40).

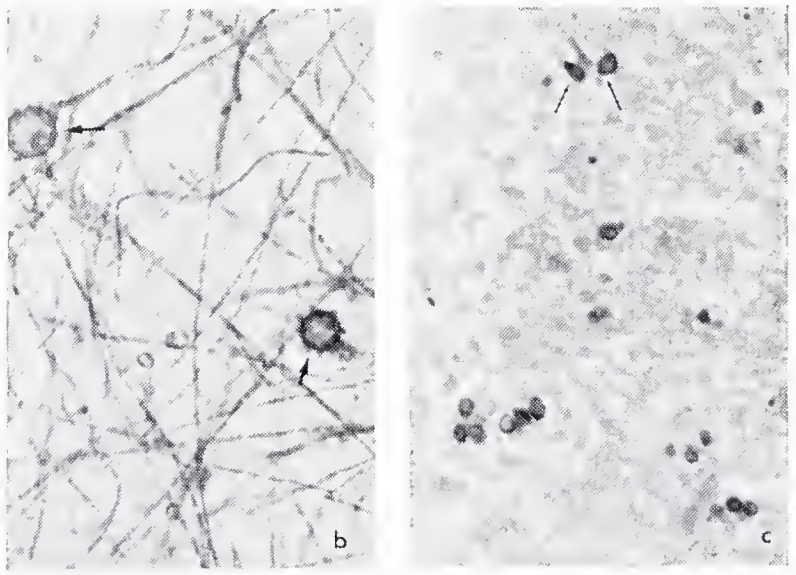

FIG. 1b: Culture of the mycelial phase of *H. capulatum*. The tuberculate macroconidia (arrows) are diagnostic (wet mount; lactophenol cotton blue, X1,000).

FIG. 1c: Yeast phase *H. capsulatum* seen in the necrotic tissue of the lymph node in Fig. 1a. Two of the organisms may be "budding" (arrows) (Gomori-methenamine silver stain, X1,000).

(Micrographs courtesy of Dr. D. W. Chamberlain, Department of Pathology, Toronto Western Hospital.)

Similar to other intracellular parasitic infections, resistance is mediated through cellular immune mechanisms. T-lymphocytes are the key defensive cells, causing macrophage activation and subsequent inhibition of intracellular growth[12, 13].

DIAGNOSIS

A definitive diagnosis of histoplasmosis can only be made after isolation of *H. capsulatum*. This may be from a variety of sources including sputum (in patients with respiratory symptoms), bone marrow aspirate, biopsy specimens of lymph node (Fig. 1a), lung, liver and spleen, and smears of mucocutaneous lesions. Demonstration of the organism is synonymous with infection as there are no documented cases of the organism being found as an incidental contaminant in man.

Skin Test and Laboratory Investigations

The skin test represents a method for detecting delayed hypersensitivity to antigen (histoplasmin) from broth cultures of the mycelial and, occasionally, yeast growth phase. The antigen is injected intradermally and the test site interpreted at 48-72 hours. A positive result is manifest by an area of induration equal to or greater than 5 mm, surrounded by an erythematous flush. The test becomes positive usually within two weeks of infection and remains positive for many years (perhaps life-long).

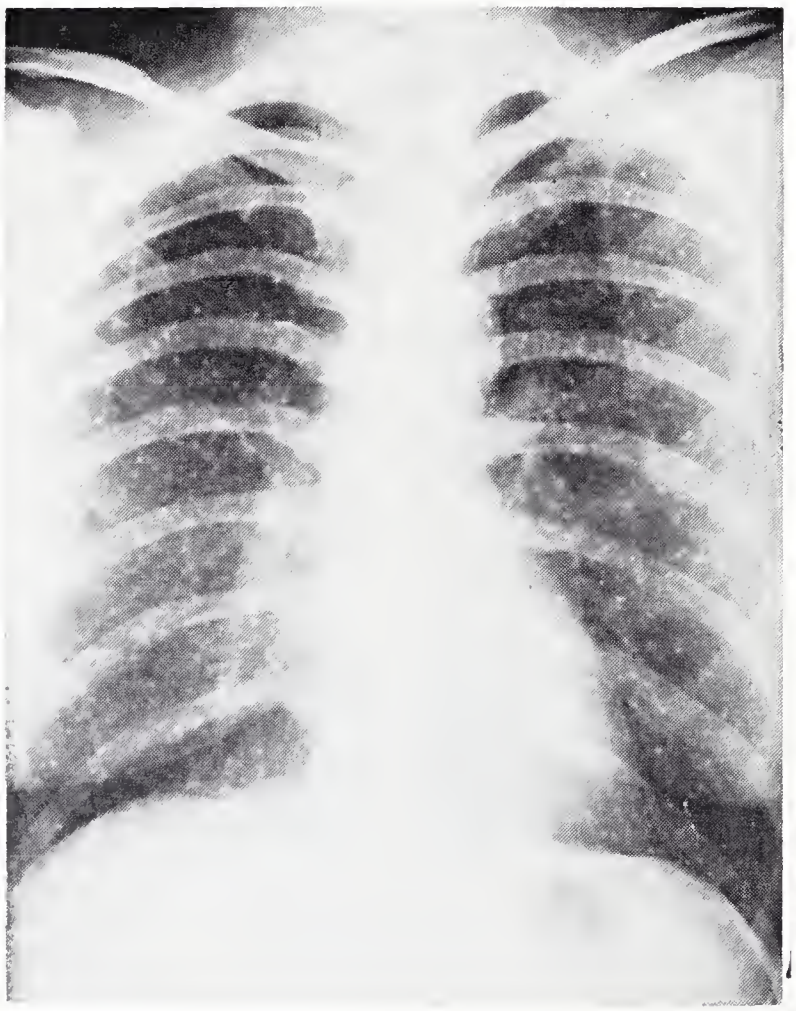

FIG. 2: Calcified miliary histoplasmosis in an asymptomatic woman. This X-ray is virtually pathognomonic of histoplasmosis and led to the retrospective diagnosis. (Figure courtesy of Dr. D. J. Wise, Department of Radiology, Toronto Western Hospital.)

The greatest usefulness of the skin test would appear to be its ability to map areas of endemicity. Its clinical usefulness is limited because of cross-reactivity with other fungal skin tests[14], high numbers of false negatives, and inability to distinguish accurately between active and inactive infection. The lack of skin reactivity in the chronic progressive cavitary and disseminated forms of the disease has been shown in numerous studies[15, 16, 17].

Serologic tests include (1) Complement Fixation tests (most commonly used), (2) Latex Agglutination tests, and (3) Precipitin (immunodiffusion) tests. Serologic tests usually become positive within a month of infection. *Blood for serology should be drawn before skin testing if possible to decrease the incidence of false positive results.* As with the skin test, serologic tests show cross-reactivity with other mycotic antigens and may be negative in the terminal stages of acute disseminated disease or chronic well localized disease. A changing titre is more significant than an absolute value because it reflects current or recent antigenic stimulus.

CLINICAL TYPES

Histoplasmosis incorporates a clinical spectrum from the relatively common, asymptomatic infection, to the rare, rapidly fatal disseminated disease.

1. *Asymptomatic (Benign) Pulmonary Histoplasmosis.* This is by far the most common result of infection with *H. capsulatum*. Inhalation of spores results in a minor pathological response and minimal or absent illness. The diagnosis is made retrospectively on the basis of positive complement fixation and skin tests, roentgenograms showing calcifications in the lung (Fig. 2) and occasionally spleen, or characteristic peripheral atrophic scars in the fundus of the eye.

2. *Acute Pulmonary Histoplasmosis.* Acute infection may be mild, in which case there is general malaise and mild fever lasting one or two days. Radiological examination may show nodular or pneumonic infiltrates with or without lymphadenopathy. In this way the x-ray mimics acute pneumonia or primary tuberculosis.

In the moderate or more severe forms of acute pulmonary histoplasmosis there is a non-specific illness resembling primary atypical pneumonia. The patient becomes ill with fever, sweats, non-productive cough and fatigue 7 to 21 days after exposure. There may also be burning chest pain, anorexia, and weight loss. The chest films show diffuse mottled densities 1-2 cm in diameter, uniformly distributed throughout both lung fields, and enlarged hilar nodes. These changes persist for 1 to 3 months, some of the lesions healing by calcification after 12 to 18 months.

Rarely, acute infection may manifest as severe respiratory failure[18] or as the progressive, fibrocavitary form of the disease more commonly associated with chronic pulmonary infection[19].

Acute pulmonary histoplasmosis carries a good prognosis, and most patients do not require specific therapy.

3. *Chronic Pulmonary Histoplasmosis.* The signs, symptoms and radiological appearance of progressive

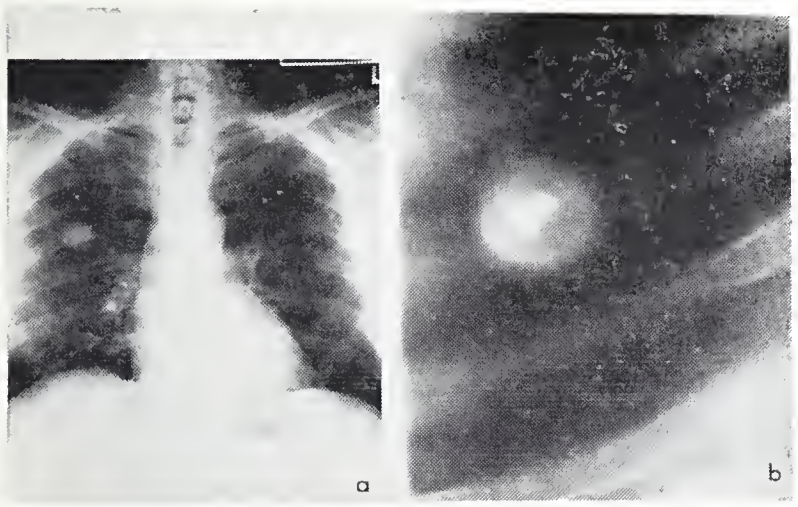

FIG. 3a: Solitary histoplasmoma and hilar adenopathy in the right lung of an asymptomatic woman.

FIG. 3b: Tomogram of the histoplasmoma in Fig. 3a. The central and concentric calcification of the granuloma is evident in this projection.

(Figures courtesy of Dr. D. J. Wise, Department of Radiology, Toronto Western Hospital.)

pulmonary histoplasmosis are identical to chronic pulmonary tuberculosis. It most probably represents endogenous reinfection as it is seen most commonly in males over the age of 40 with a higher incidence among farmers. The patient presents with chronic cough, mucopurulent sputum, malaise and mild fever, chest pain, weight loss and fatigue. Fibrosis of pulmonary lesions may lead to tracheal deviation to the maximally involved side. Also reported are broncholiths (due to breakdown of calcified hilar nodes which subsequently discharge into a bronchus), "middle lobe syndrome", bronchiectasis and superior vena cava obstruction by a compressive mediastinal mass.

The most frequently seen radiological findings are one or more calcified or partially calcified foci in the pulmonary parenchyma and mediastinal lymph nodes. This may be accompanied by cavitation (usually of the upper lobes), extensive fibrosis, consolidation and volume loss.

Another common finding is the solitary histoplasmoma. In a Veterans' Administration-Armed Forces study, Steele[20] found it to be the most common in a series of 392 resected granulomas. On x-ray the histoplasmoma resembles other "coin" lesions in that it is 1-4 cm in size, solitary, and may enlarge mimicking a neoplasm (Fig. 3a). Usually it calcifies, often concentrically with a central focus (Fig. 3b), or in a laminated or stippled ("mulberry type") manner described by Sutaria et al[21]. Some patients may go on to develop multiple pulmonary nodules ("benign progressive multinodular histoplasmosis"[22]).

Chronic pulmonary histoplasmosis usually runs a progressive course over years with remissions and exacerbations due to chronic reactivation. Two major complications include superimposed acute or chronic pulmonary infections with klebsiella, *Staphylococcus aureus* or acid-fast bacilli, and emphysema. A poor prognosis is more commonly the result of an associated complication than the disease process itself.

4. *Disseminated Histoplasmosis.* More important than the insignificant hematogenous dissemination of the acute form of pulmonary histoplasmosis is the massive, acute or chronic dissemination rarely seen in the very young, old, or debilitated patient.

Acute disseminated histoplasmosis is seen most often in young infants and presents as an abrupt systemic illness with low to moderate irregular fever, hepatosplenomegaly, weight loss, emaciation, hypochromic anemia, lymphadenopathy, leukopenia, albuminuria and lesions in the lung. There may be ulcers of the skin, oropharynx and larynx, and enterocolitis.

The diagnosis must be made on the basis of examination and culture of tissue and body fluids because skin and serologic tests are often of no value in this stage of the disease. Untreated, acute disseminated histoplasmosis runs a rapid downhill course to death.

Chronic dissemination is more often seen in the elderly and usually in patients suffering from other chronic debilitating diseases. In such cases it is common for the adrenals to be invaded and destroyed (Fig. 4). There is massive caseous necrosis resulting in the characteristic clinical picture of primary adrenocortical insufficiency. Sarosi et al[16], in a description of 54 cases of disseminated histoplasmosis, showed significant adrenal insufficiency in 50%. The development of adrenal hypofunction was associated with markedly increased mortality, emphasizing the importance of careful and repeated adrenal function tests. Other signs of chronic dissemination include hepatosplenomegaly, and positive blood cultures.

FIG. 4: Adrenal gland at autopsy from a 73 year old man with generalized (disseminated) histoplasmosis involving many organs including the adrenals, kidneys, spleen, larynx, cerebrum, stomach, jejunum and ileum. He was in a "shocked" state terminally and death was due to the generalized histoplasmosis with superimposed bacterial bronchopneumonia. The adrenals on gross inspection were yellow-white and showed a complete loss of normal cortical and medullary architecture. (Photograph courtesy of Dr. J. B. Walter, Department of Pathology, Toronto General Hospital.)

5. *Extrapulmonary Histoplasmosis.* Localized extrapulmonary histoplasmosis results most commonly from hematogenous dissemination, but in rare cases it may result from primary infection. The areas of predilection include:

Eyes – Ocular histoplasmosis, presenting as chorioretinitis, was first described by Krause and Hopkins[23] in 1951. The diagnosis of ocular histoplasmosis is always "presumed" because the organism has yet to be seen or cultured in the fundus lesions. Involvement is manifest by (1) peripheral atrophic scars, representing inactive histoplasmosis, and which are present in large numbers of the population in endemic areas; (2) circumpapillary choroiditis; and (3) macular and paramacular lesions which result in significant visual impairment. Ocular lesions are most common in the 20 to 50 age group, and are frequently found in patients with minimal or absent signs of pulmonary infection. Skin testing with histoplasmin is contraindicated in the presence of macular lesions as it is known to aggravate these lesions and lead to further visual impairment[24].

Skin – Cutaneous or mucocutaneous histoplasmosis has been observed as a well-localized, chancre-like lesion with regional lymphadenopathy. Erythema multiforme in association with histoplasmosis was first described by Leznoff et al[11], and erythema nodosum has been documented by Baum et al[25].

Ear, Nose and Throat – Nasal-oral histoplasmosis may simulate rhinoscleroma, laryngeal tuberculosis, aleukemic leukemia, lymphoma, blastomycosis, syphilis and squamous cell carcinoma. Involvement of the ear may result in a non-specific otitis media. A careful search will reveal the characteristic intracellular organisms.

Heart – Histoplasmosis has on rare occasions been the cause of a vegetative endocarditis, usually involving the aortic valve. Gwinn et al[26] described a 15 year old girl with a calcified pericardium secondary to histoplasmosis. This was one of several cases of pericarditis associated with past or active infection with *H. capsulatum*.

Gastrointestinal Tract – Ulcerative enteritis due to histoplasmosis can occur through hematogenous spread and rarely by drinking water contaminated by *H. capsulatum*.

Brain – Cerebral histoplasmosis, presenting as meningitis or focal histoplasmoma, is usually the result of hematogenous dissemination.

Other Sites – Many other organs may be involved, including the kidneys, prostate and joints. Class and Cascio[27] described a case in which migratory polyarthritis was the predominant clinical manifestation.

DIFFERENTIAL DIAGNOSIS

Owing to its many forms of clinical presentation, histoplasmosis closely resembles many infectious and granulomatous diseases. Pulmonary tuberculosis is by far the most important and it must be excluded before a diagnosis of histoplasmosis is made.

In comparison to pulmonary tuberculosis, progressive pulmonary histoplasmosis is less likely to progress; it is more likely to cause significant distortion of pulmonary achitecture through calcification, fibrosis, necrosis and cavitation; and it is more likely to result in pulmonary insufficiency. In summary, *"anything tuberculosis can do, histoplasmosis can do better"*.

Progressive pulmonary histoplasmosis may also resemble other fungal diseases including coccidiodomycosis, cryptococcosis and blastomycosis; benign or malignant primary or metastatic tumour; chronic lung abscess; bacterial pneumonia (especially klebsiella pneumonia); bronchiectasis; and hamartoma.

The differential diagnosis of acute pulmonary histoplasmosis includes primary atypical pneumonia, psittacosis, Q fever, influenza and bacterial pneumonia. Disseminated histoplasmosis imitates other systemic causes of fever and prostration, and is seen frequently in patients with Hodgkin's disease and other neoplasias of the reticuloendothelial system. Chronic extrapulmonary histoplasmosis may simulate a myriad of diseases and conditions depending on the site(s) of localization.

TREATMENT

The majority of cases of benign pulmonary histoplasmosis heal spontaneously and *do not require therapy*. Treatment is indicated in all cases of progressive pulmonary, disseminated and symptomatic extrapulmonary histoplasmosis.

Amphotericin B, derived from a species of streptomyces fungus, is still the best available anti-fungal agent. The drug must be administered by a continuous intravenous drip in doses which are often toxic. The most common side effects are azotemia, anemia, venous phlebitis and thrombosis, fever, chills, headache, nausea and vomiting.

The total dose of Amphotericin B required depends on the clinical type of infection and has not yet been satisfactorily established. Sutliff[28], treating chronic pulmonary histoplasmosis, concluded that a total dose between 0.5 and 2.5 gm given over 3½ to 17 weeks would be useful in controlling infections and minimizing toxic reactions.

Sarosi et al[16] and other investigations[17, 29] found that survival in disseminated histoplasmosis was correlated with early and large dose (up to 38 mg/kg) Amphotericin B therapy.

Amphotericin B in combination with corticosteroids[24] and corticosteroids with photocoagulation[30] have been useful in the treatment of ocular histoplasmosis with macular involvement.

Surgery is most valuable in the management of chronic pulmonary histoplasmosis. In a report of 155 patients treated with surgery over a twenty year period, Saab et al[31] found surgery to be useful in removing residual, localized lesions and foci of infection in fibro-cavitary histoplasmosis. Surgery was also used to treat unresolved pulmonary infiltrates, mediastinal granulomas, and for definitive diagnosis of solitary nodules. In the surgical management of cavitary histoplasmosis, pre- and post-operative Amphotericin B therapy was associated with decreased long-term mortality and progression of the disease, but a higher incidence of immediate post-operative complications.

SUMMARY

Histoplasmosis is a fungal disease endemic in regions of Ontario and Quebec. The majority of infections are benign and asymptomatic, but symptomatic infection may present with varied clinical manifestations that closely resemble tuberculosis. Amphotericin B is still the best therapeutic agent available; however, its administration is commonly associated with toxic side effects.

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Teenage Smoking: A Toronto Study

Warren Rubenstein, 7T5

In January, 1963, the Surgeon-General of the United States unleashed a bombshell on an unsuspecting public, reporting the strong relationship between cigarette smoking, lung cancer and other pulmonary and cardiovascular diseases. Since that time both medical and lay health organizations have bombarded the country with advertising campaigns warning of the hazards of smoking, threatening a life of ill health or early death as its result. Later, government agencies joined the parade by producing legislation requiring warnings on cigarette packages, outlawing cigarette advertising on radio and television and raising taxes on cigarette sales to enormous levels. All this was to apparently no avail. Per capita cigarette consumption in Canada has increased[7]. The tobacco industry and its lobby are thriving. They have turned their advertising funds to sponsoring professional spectator sport. Finally, despite massive education programmes in and outside of the schools, there is an acknowledged increase in smoking among the teenage population.

In the late 60's and early 70's, several studies were published in Canada and the United States to document and analyze smoking habits among teenagers.[1, 2, 3, 4] They all validated the suspicion that teenage smoking was on the upswing. This study was undertaken to view the trends in 1974 and attempt to understand environmental influences and the effect of the school health education programmes on today's teenager.

METHOD

A questionnaire was distributed to teenagers in two locations: the Teen Clinic of the Hospital for Sick Children (HSC) in Toronto, and the private office of Dr. Martin Wolfish (then head of the Division of Adolescent Medicine at HSC), whose practice is restricted almost entirely to adolescents. The clinic at the hospital serves predominantly the lower socio-economic group in downtown Toronto. Dr. Wolfish's office, located in suburban Toronto, serves the higher economic classes. The questionnaires were distributed at random by the nurses when patients first arrived in the clinic or office. They were allowed to fill out the questionnaire unattended in the adjoining waiting rooms and then returned them to the nurse, who fielded any questions. A total of 125 questionnaires were completed.

In interpreting the results of the survey, there was no attempt to perform complicated statistical analyses. The scope of the survey was limited and its goals modest. Many of the results show such obvious trends that interpretation is simple. In other cases, comparison will be made to the longer, more sophisticated studies previously mentioned.

Two of the most common questions that arose in relation to the questionnaire should be clarified here:

a) "smoking" referred only to *cigarette* smoking.

b) "Age of onset" referred to onset of the person's regular smoking habits, not the first experiments with cigarettes.

RESULTS

Total Smokers

In the total group, that varied between ages 10 years to 19 years, 60.8% classified themselves as smokers. But it is interesting to break down the percentage of smokers vs. non-smokers in specific age groups. As seen in Figure I, the ratio of smokers to non-smokers is directly proportional to age.

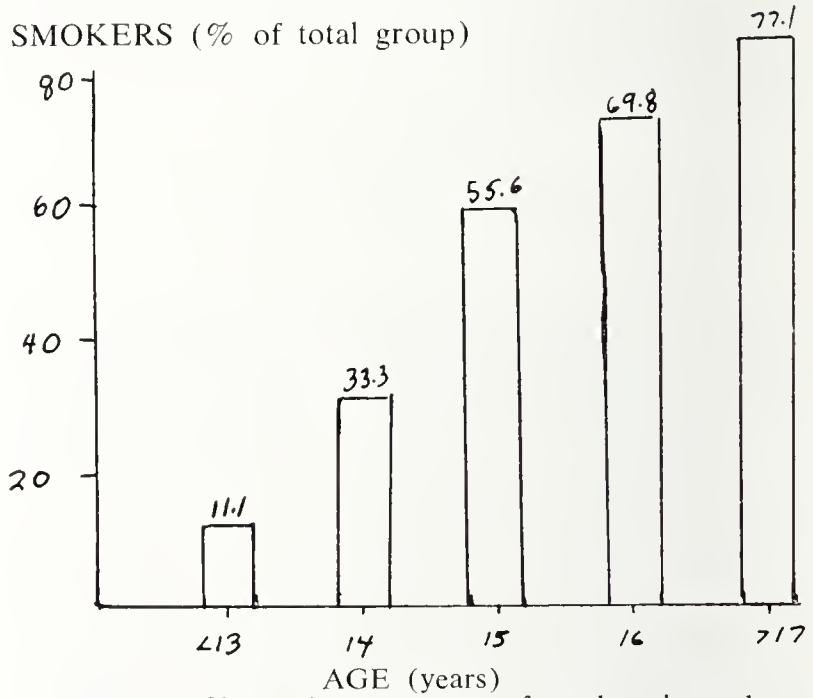

FIGURE I: Shows the percentage of smokers in each age group.

Age of Onset

Figure II shows the age at which the smokers adopted the habit regularly. There is no remarkable peak at any particular age and there is uniformity through the early teenage years. But it is important to note the marked decrease in new smokers after the age of 15.

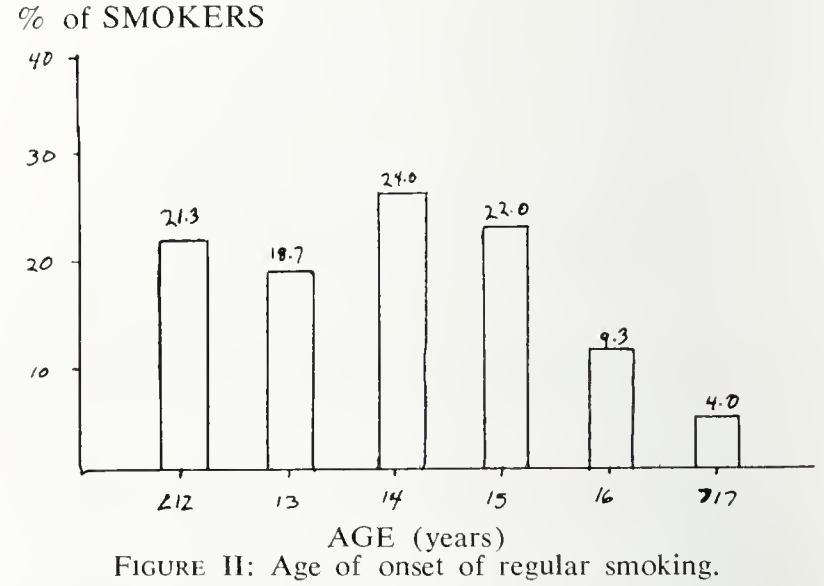

FIGURE II: Age of onset of regular smoking.

Family and Peer Group Influence

Table I lists the members of each teenager's family who smoke. There is very little difference between the numbers of smoking and non-smoking teenagers in

families where one or both parents smoke. It might be concluded (with hesitancy because of the small numbers) that the fact that one or both parents smoke would not make it more likely that the teenager in the family also smokes. But, where at least one sibling in the family smokes, chances were four times greater that the teenager questioned also smokes.

TABLE I: Other smokers in the family

	Smokers	*Non-Smokers*
One parent only	13	17
Both parents only	3	4
One parent and at least one sib	27	7
Both parents and at least one sib	16	3
Sibling(s) only	9	1
No other smokers	8	17

According to Table II, 85.5% of smokers indicated that "many" of their friends also smoked. But only 32.7% of non-smokers indicated that "many" of their friends smoke. It is interesting to look at the 25 families who had no *other* smokers. Of these 25 families, 8 had a teenage smoker in our survey. Of these 8 teenagers, 6 (75%) responded that "many" of their friends smoke. The other two replied "few". Of the 17 other teenagers who came from non-smoking families and were themselves non-smokers, only 6 (35.3%) replied that they had "many" smoking friends and the rest had few or none.

TABLE II: "How many of your friends smoke?"

	Smokers	*Non-Smokers*
Many	85.5%	32.7%
Few	14.5%	51.0%
None	0	16.3%

Knowledge of Health Hazards

In a direct yes or no question, 95.2% of those surveyed answered YES, smoking is dangerous to your health. They were then asked to list in space provided any "health problems that may result from smoking." The results in Table III show that the vast majority (75% of smokers and 90% of non-smokers) considered lung cancer a problem related to smoking. Emphysema ranked second, being mentioned on about 30% of questionnaires. Other diseases in the cardiopulmonary systems were mentioned by about 10% of those surveyed. Non-smokers fared only slightly better in the knowledge of health hazards than did the smokers.

TABLE III: Diseases listed by those surveyed as health problems related to smoking.

Diseases	*Smokers* %	*Non-Smokers* %	*Total Group* %
Cancer	75	89.8	78.4
Bronchitis	8.1	8.2	8.1
Emphysema	29.1	22.4	26.4
Heart Disease	13.2	18.4	15.3
Cough, Sore Throat	13.2	8.2	11.2
Shortness of Breath	8.1	10.2	8.8
Bad Breath	1.3	2.0	1.6
T.B.	1.3	–	0.8
Other	2.6	14.3	7.2
No Answer	10.4	8.2	9.6

Other Interesting Results

1. In response to where they first began smoking, 90.9% of smokers indicated that they began with friends as opposed to 7.8% at home.

2. About 80% of smokers smoked greater than 5 cigarettes per day.

3. Why do these teenagers smoke? When given blank space to answer this question, 80% of the answers were classifiable into three groups (see Table IV).

TABLE IV

Reasons for Smoking	*% of Total Group*
Social pressure	7.4
Relaxing, enjoyable	43.2
Habit	28.4
No/Other reason	21.0

DISCUSSION

As mentioned previously, several large studies have been published discussing smoking among teenagers. Results tend to vary widely because of differences in definition, regional differences, etc., but the trends indicated are conclusive. Although the numbers in this study are small and the population relatively select, the results indicate a possible direction for further anti-smoking campaigns with this age group.

This study has reported a remarkably high percentage of smokers in its sample: 60.8%. The large Canadian School Survey[2] did not establish a general figure. But the Canadian Department of Health and Welfare[1] has published general figures for teenage smoking. In a report dated September 26, 1973, they reported an increase in the percentage of smokers in the 15-19 age group from 31.5% in 1965 to 37% in 1972.

The American Bureau of Census states that across the nation about 15% of teenagers between the ages of 12-18 are cigarette smokers[3]. It is important to consider possible explanations for the high figures in this study. The majority of adolescents presenting to the HSC Clinic and Dr. Wolfish's office do so for specific complaints or problems rather than routine physical examinations. This study thus represents a specific subgroup of the general teenage population that has "problems" of one kind or another. Thus, it would seem that the adolescent with psychosocial problems, obesity, requiring abortion or birth control counselling or with chronic ill health is more likely to be a smoker. Perhaps he/she takes up smoking for the main reason listed in Table IV – to find a relaxing or enjoyable escape from the other problems. Another possible explanation would be that smoking creates health problems in the teenager bringing him into the health care system. Finally, it should be re-emphasized that the three studies mentioned above all document a definite increase in teenage smoking over the last decade.

Furthermore, this study, like previous investigations, indicates that regular smoking begins about age 13-15, although it is common for many youngsters to experiment with a few puffs at much younger ages[5]. To meet these age limits, anti-smoking programmes in schools were begun earlier and earlier, presently established at the Grade VI level. If these programmes succeed until the child is 15 years of age, this study shows he is less likely to take on the habit, at least in the next few years. McKennell et al, and Salter and Obelen in 1967 showed that a person who is a non-smoker at the age of 20, is almost surely to be a non-smoker for life[2]. Thus, it

would appear that a person's smoking habits for life are established by age 15.

It had been an established fact in the studies quoted above that the more people that smoke in the family the more likely it was that the teenager also smoked. The Canadian School Survey[2] indicated that the one factor that made the greatest difference in whether the teenager smoked or not was the presence of at least ONE smoking parent. The addition of other family members made little difference. James reported that if both parents smoke, the teenager is twice as likely to be a smoker[3]. In addition, if an older brother or sister smokes, the teenager is twice as likely to be a smoker. This study looked at peer influences as well and seemed to indicate that peer influence was stronger. This should not be surprising considering today's teenagers' reputation for rebellion and independence from their parents.

(Recently the Canadian Cancer Society began to distribute a new educational tool with peer influence in mind. This "Celly" kit stresses the hazards of smoking in a subtle way, but which may be understood by children from kindergarten to grade three. It encourages the child to come to his/her own decision about smoking.)

Finally, the above studies attempted to evaluate the effect of "anti-smoking" education programmes. For many years the goal was to educate the teenager about the health hazards of smoking and thereby frighten the young person. The Canadian School Survey concluded that the students are generally knowledgeable about the hazards but then said only 50% *believed* smoking causes lung cancer[2]. A study in the *Lancet* showed that teenagers know about the relation to lung cancer but little about other smoking-associated diseases[6]. This is confirmed in our present study. Furthermore, the other two studies show a better knowledge among non-smokers than smokers. This was not confirmed here. It must be concluded from this information that anti-smoking education programmes have apparently failed. The information has had little deterrent effect on teenage smoking habits.

It has been postulated that teenagers cannot readily accept these hazards as pertinent to them because they do not present until much later in life. But, recently it has been shown that smoking brings about early pathological change in the lungs of the young smoker. Emory states that new alveoli form until the age of twenty by "alveolarization" of terminal bronchioles[7]. Cigarette smoking leads to developmental arrest by damaging small airways. Seely et al plotted mid-expiratory flow rates against maximum expired volumes and showed differences in the curves of smokers and non-smokers[8]. Smokers have lower flow rates at mid vital capacity and at lower lung volumes. This reflects small airway obstruction in smokers. Niewoehner et al reported an increased incidence of pathological changes in lungs of young smokers (autopsy specimens) and classified this change as a respiratory bronchiolitis[9]. Seely also reported in his study of high school students with 1-5 years smoking experience a much greater incidence of cough, increased sputum production and shortness of breath in the smokers. Perhaps information such as these early pathological changes and the uncomfortable side effects listed here will be more influential in the teenager's decision about smoking.

It should be noted that 43% of the teenagers said they smoked because it was "relaxing or enjoyable". In the *Lancet* article, it was reported that those teenagers who smoked to "relieve nervousness" (34%) were less likely to stop than those who started for other reasons[4]. The image of smoking as a tension reliever was one TV and magazine advertisements strived to depict. It will be interesting to discover if, with the passage of time, the abolition of these commercials will have an effect on this image of smoking.

As a final anecdote – both the Canadian School Survey and the *Lancet* study showed that academic achievement in teenagers was inversely proportional to the amount smoked.

CONCLUSIONS

Health and education organizations must

1. acknowledge the increase in teenage smoking and the futility of continuing anti-smoking programmes as they presently stand.
2. establish new programmes to emphasize
   a) present concepts of smoking-related diseases
   b) immediate pathological lung changes
   c) personal discomforts such as cough, dyspnea and bad breath
   d) that the decision whether to smoke or not should be a carefully considered individual decision, not subject to external pressure, since it is the individual who must bear the consequences.

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Kids and Cancer (Part 2) *

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The Parents

In Part I of this article, we examined the reactions of children to chronic illness and impending death, as exemplified by cancer. We discovered that such reactions are age-dependent; that in the older child, they may be phasic (anticipatory, impact, recoil, and post-traumatic); that they are both direct and reactive, and affect personality, body image, and response to treatment; that they may occur in an orderly sequence (denial, anger, bargaining, depression, and acceptance); and that the adaptive outcome depends on a number of interacting factors.

One of the most important of these factors is the family, for the illness of a child with a chronic (or acute) disease both affects and is affected by the interpersonal family equilibrium of which he is a part. In addition, since the physician cannot change the reality of the situation, he frequently feels unable to lessen suffering within the family unit. However, understanding the nature of the stress from this viewpoint, and appreciating that there are characteristic ways in which the family copes with the situation, should enable the doctor to offer helpful support. Let us now turn, therefore, to the focus of this sphere of consideration, namely, the parents[1].

EARLY REACTIONS

Many parents actually suspect that their child might have cancer before hearing it from a doctor, but upon being given the definitive diagnosis, react in one of two ways — shock ("stunned") or denial[2]. And even those who are initially "numb" eventually hope that the diagnosis is wrong. The phase of disbelief usually persists for a few weeks. If, at this point, the child is admitted to a treatment centre, and if his particular type of neoplasm is possibly or probably incurable, a discussion of the limitations of therapy may invoke an immediate reaction of hostility (e.g., "Only God can decide my son's future"). However, after a few days to a few weeks, most parents will be thankful for this approach, because it means they have "heard the worst", and can therefore have the confidence to master subsequent, less devastating developments. Eliminating the fear of the unknown discourages unrealistic and maladaptive behaviour patterns.

Almost without exception, parents pass into a phase of guilt, associated with self-recrimination, fear, frustration, and depression. In some families, there will be intensified marital strife, as parents attempt to deal with the above feelings by blaming each other, the doctor, or others. Whether this guilt is to be transient or fixed for a long time is difficult to predict, because certain families respond well to reassurance from the physician that they have not neglected their child and that the prognosis in some instances is little affected by the date of diagnosis. If the premorbid attitude has been one of over-indulgence or over-protection, then the tendency will be towards a more refractory type of guilt.

The third phase of early reaction consists of inquiry and information-seeking. This takes place by exchanging information with parents of other similarly-affected children (to a very large extent), by listening to friends and relatives, by "digging up" newspaper and magazine articles, and (to a comparatively small degree) by discussing therapeutic development with the physician. The behaviour can be understood partly as a realistic attempt to learn as much as possible about the disease in order to better master the situation and care for the ill child. But this process is constructive only to a point, and a sudden upsurge of parental questions often reflects increased anxiety or conflict, which cannot be resolved by the acquisition of more detailed information.

ANALYSIS: DEFENSE PATTERNS AND COPING MECHANISMS

The term "coping behaviour" denotes the mechanisms used by an individual to meet a significant threat to his psychological stability and which enable him to function effectively. Such behaviour would consist of environmental response as well as intra-psychic processes.

The "shock" of learning the diagnosis, as has been mentioned, is also associated with a lack of emotion ("numbness"). This may be considered as an extreme isolation of affect, a mechanism by which the intellectual recognition of a painful event does not have a concomitant intolerable emotional response. Only after hours or days is there profound emotional feeling linked with the awareness of what has happened, and this only after the necessary arrangements have been made for the child's treatment. The reduced affective experience continues in some, to be a conspicious defense, and enables parents to talk realistically about their child's condition and prognosis.

Information-seeking and concern over details of the progress of the disease (e.g., requesting Hb or WBC counts) do serve a function by allowing the parents (and doctors) to avoid the more general, and hence tragic and threatening aspects of the case. However, more anxiety is probably generated overall than dissipated by this practice.

Another defense is denial — the intellectual disclaiming of a painful event or feeling. If this is going to be protracted, then the parents will seem not to "understand" the importance of various procedures and therapeutic plans, and will therefore be prone to direct hostility towards the physician. Such people always have a history of similar defense patterns during past episodes of stress.

* See Vol. 52 No. 1 for Part I

Motor activity (e.g. sewing, knitting) sometimes serves a coping function since it physically removes the parent from the threatening situation and gives him/her "something else to think about and do".

Regarding social influence, the major source of emotional support for most parents during the period of hospitalization is other parents. They learn from each other, and can profit by observing others successfully, albeit painfully, go through the experience of having a terminally ill child.

Parents generally find it intolerable to think of their child's cancer as a "chance" or meaningless event. Therefore, they try to construct an explanation for it, displaying some urgency about it until one that is appropriate and acceptable can be found. In the process, they compose an immediate and definite answer which is a mixture of scientific fact, elements from the parents' past experiences, and fantasies. Tied to this is comfort derived from religious belief. Although a small minority of parents have questioned their faith as a result of the experience, most find that it makes things at least more acceptable, if not understandable.

Finally, hope — defined as the expectation of a favourable alteration of the awaited sequence of events — is also of general clinical importance, and is universally emphasized by parents. Unlike massive denial, hope does not appear to interfere with effective behaviour. That the persistence of hope does not require the need to intellectually deny the child's prognosis ("Without hope I could never keep going . . . though I know deep down that nothing can really be done") is significant, for it differentiates hope from other defense patterns that may potentially distort reality.

SOME FURTHER PROBLEMS

Two further problems concern the hospitalized child, and the child in remission. With younger children especially, after they have been ill for some time, there will be rejection of parents, sometimes quite openly ("I hate you and I don't ever want to see you again"). This seems partly related to the parent's inability to prevent painful procedures and prolonged hospitalization. Consequently, there is damage to the usual childhood faith in parental omnipotence. Furthermore, it is possible that the child senses his dependence on the medical and nursing staff, and is therefore afraid to express hostility toward them. In essence, then, young children perceive a transfer of authority from parents to professional staff. The results of this are two-fold — a feeling of failure and uselessness on the part of the parents, and a feeling of hostility towards the staff.

Secondly, the child in remission poses a number of management problems[3]. When at home, parents may fear the onset of some acute medical problem which they would fail to recognize — perhaps reminding them of past inadequacies concerning the original symptoms and re-awakening feelings of guilt and neglect. And discipline can go to one of two- extremes, over-indulgence or over-protection. The former arises out of a fear of denying any pleasure and hence of setting any limits. Sibling rivalry is thus easily evoked. The latter arises out of a fear of exacerbating the illness and can lead to an isolated, unnecessarily restricted home life.

THE TERMINAL PHASE

As the disease progresses, there is a reciprocal curtailment, dissipation, and narrowing of hope, and a rise in "anticipatory grief". The signs and symptoms of this anticipatory mourning process may consist of apathy, weakness, preoccupation with the ill child, or somatic complaints on the part of the parents. Sighing is frequently observed, as is nocturnal crying and a generally depressed appearance. There may be an agitated depression, wherein the parent talks for hours about the child, or engages in increased motor activity, including care of the other ward children.

When all established therapeutic agents have been exhausted, there is an acceleration of "grief-work" or an actual precipitation of mourning. In spite of a generally appreciative attitude regarding visits by the physician, there is also less understanding, more annoyance at even minor variations in response to treatment, and frequent, though brief, expressions of anger.

When the child's death comes, it will most often be taken calmly, with the appropriate expression of affect. Outbursts of uncontrollable grief are the exception, and usually there is some indication of relief that the child is no longer suffering.

The cessation of the child's life does not, therefore, appear to be a superimposed stressful situation, but rather an anticipated loss at the end of a long sequence of events.

IMPLICATIONS FOR PHYSICIANS AND CONCLUSIONS

Each parent of a child with a fatal disease reacts to the tragedy in a unique manner. However, when the illness is cancer, they share many similar problems that are inherent in the situation, and certain modes of adjustment commonly occur in a characteristic sequence. Though parental behaviour is not stereotyped, it is therefore predictable to some degree.

Usually, most parents are unable to incorporate detailed information regarding the disease and its clinical course during the first days after the diagnosis. The physician should therefore confine his guidance to the immediate problem and acute condition. Sufficient time and privacy should be available later to allow parents to

ask their questions, even repetitiously, since this is one of the processes by which they come to accept the diagnosis. And if referral to a large medical centre is contemplated, the parents should be given realistic expectations.

After this, the parents should be furnished with sufficient information about cancer to allow them to realistically help in the care and handling of their child. Such information also aids them in resolving any feelings of guilt or sense of responsibility for their child's illness. However, requests for detailed medical data, such as daily lab findings, should be discouraged and evaluated in terms of what underlying needs the parents are attempting to fulfill.

The physician should appreciate the attempts of parents to find some "meaning" or "cause" for their child's illness, and so unrealistic etiological explanations should only gradually be questioned.

The parents should be informed that apathy, depression, and overt hostility are often the natural consequence of prolonged illness and hospitalization in children.

At the time of discharge, parents should be reassured regarding their adequacy to meet the demands of the situation, and special emphasis should be paid to discussing what activities are reasonable for the child, with the aim of preventing undue restrictions and overprotection.

In summary, coping mechanisms observed in parents should be viewed in terms of how such behaviour contributes to, or interferes with meeting the needs of the ill child and other family members, yet not neglecting the protective function that such behaviour has, in keeping anxiety and depression within tolerable limits for the individual parent.

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The Physician

In the first section of this article, we examined the reactions of parents to having a child with a terminal malignancy. We discovered that the early responses are phasic (shock/denial, guilt, inquiry); that they, as defense mechanisms, contribute to a pattern known as "coping behaviour"; that this pattern also includes motor activity, social influences, religion, and hope; that the hospitalized child and the child in remission pose problems of their own; that the terminal phase may evoke relief rather than stress; and that because parental behaviour is predictable to a certain degree, the physician is in a position to intervene at stressful points and offer support.

Perhaps the most strategic point of all is right at the beginning. For it is at the diagnosis stage that the physician has his greatest impact, and it is from that stage that all future interventions shall stem. It is the purpose of this final chapter, then, to examine the question of whether, when, and how the patient shall be informed of his illness, and in answering them, to formulate an approach to the dying child.

PHYSICIAN, PROTECT THYSELF

It is an integral part of being a physician to face the dying and to help the patient and his family meet the situation. But by and large, physicians in recent years have sought to protect the dying from becoming aware of their fate. Perhaps many who enter medicine are particularly afraid of dying and transfer their own concern to their patients. Considerable literature has emerged which indicates that the doctor, in trying to protect the patient, often *over*protects him, creating serious difficulties, and may, in fact, be protecting *himself* from an unpleasant and painful situation[1].

After all, physicians are oriented primarily to the cure of illness. The recognition and handling of death is the very antithesis of this orientation. And doctors, not being immune to their own feelings, fears, and anxieties, feel obliged to "protect" the patient from anything that would cause him undue concern. One study[9] indicates that although physicians think less about death than do control groups of patients and non-professionals, they are more *afraid* of death. Thus, the doctor considers his own fears about death, puts them as intellectual questions, and tries to answer them for other people. By having the power to cure, he obtains dominion over his own anxiety.

Physicians often rationalize their attitude with: "In my experience, to tell a patient he has cancer deprives him of hope and inevitably leads to a severe depression and withdrawal." Actually, the doctors are afraid to relinquish their role as healer. They frequently resort to pseudo-diagnosis, with which both patient and doctor can maintain an illusion of curability. Occasionally, when forced by the patient or circumstances to reveal the true illness, some physicians become so anxious that they act in inappropriate ways, one of the worst being abandonment of the patient. The depressions the doctors fear are traumatic indeed, but they are the result of preventable gross stress reactions (see Part I), not impending loss or death[2].

Therefore, in order to help a child cope with the problems of serious disease, it is necessary to develop an environment in which he feels safe to ask any question, and confident of receiving an honest, complete answer.

A CANCER WARD[3]

When a death occurs on a pediatric oncology ward, the true nature of the event is known to every child, for these hospital-wise children quickly learn to interpret the meaning of the sudden absence of a playmate, the removal of an oxygen tent, a missing nameplate, a room change in the middle of the night, and even the disconnection of a Bird respirator. So that if a child dies, and a playmate asks the question, "What happened to Johnny?" answers like, "He went home", "He went to another hospital", or "He went to another floor", are only superficially accepted, not really believed. If and when they are, the results can be quite poignant. For example, patient B, age 9, had frequently received the reply that certain children "had gone to the 13th floor." One day, because of space limitations on the ward, it became necessary to transfer him to the 13th floor. The child suddenly became completely unmanageable, and displayed such panic and anger that he had to be restrained to protect himself and others. It took over an hour to learn that he didn't want to go to the 13th floor because, "That's where kids go to die." He went on to explain, "When kids get sent to the 13th floor I never see them again."

The moral of this example is that children are very acutely attuned to the wavelengths of this environment. Consequently, when this environment signals that certain subjects are not to be discussed, and may be too painful for the adult to deal with in a manner which transmits some degree of strength, the child becomes mute, outwardly accepting the adult's words, but inwardly feeling abandoned. He is left to cope with his fears and anxieties by himself at the very time when he needs and seeks all the strength and support available.

Since children may not ask questions of the staff or their parents, the initiative for talking about death must come from the adult who is in possession of more emotional strength. This will demonstrate to the child that the staff member can talk comfortably about those worries which are of paramount concern to him. At the same time, the child is able to gain strength from the realization that he is not so sick as, say, his friend was before death. (Hence, staff should approach a child after there has been a death on the ward, as soon as possible, with a statement like, "Johnny died last night. He was very sick.")

Even the child who is gravely ill can benefit by the staff's sympathetic recognition of the seriousness of his situation, for every child is worrying about dying, and is eager to have someone help him talk about it. If he is passive, it may only be a reflection of how freely the environment encourages him to express his concerns.

TO TELL THE TRUTH

Because a child's concept of death is highly age-dependent (see Part I) it is probably wise to use the approximate figure of 9-10 years as a time at which an attempt to explain the diagnosis should be begun. Depending on actual age and background, the manner in which the patient is told might emphasize the following points: The child should be given some idea of the chronicity of the disease. Having been informed that he may have to spend a lot of time in hospital, he should then be assured that treatment will help him feel well enough to return to normal activities. And the older child can gain support from knowledge about research efforts. Naturally, the details of each explanation will also depend on the type of neoplasm involved.

Studies have shown[4] that children accept such an approach without untoward reaction, and even, in many cases, with relief. The potential tragedy of trying to erect a wall of secrecy can be illustrated by the following example[5]. Patient D, age 16, wasn't told his diagnosis by his mother until 12 hours before he died. His mother had used almost all her energy manipulating the environment to keep it a secret, and had found it very hard to communicate with her son throughout the 6 months of his illness. Finally, he had asked her if he had leukemia, and she answered, "Yes." He turned to her, relieved, and said, "Mother, I knew it all along." Patient D had spent the last 6 months of his life denied the emotional strength that his mother could have provided if she hadn't been so busy trying to hide the truth. She could have done this while her son was still in remission and feeling well, but by the time an adequate mother-son relationship had been re-established, his life was over.

Other factors to consider are that failure to discuss the diagnosis with the child may contribute to behaviour problems. Secondly, the disease and its implications should be shared freely with all members of the immediate family, especially the siblings, for such children also perceive quickly that something serious has occurred, and special treatment which the patient receives may be strongly resented. And thirdly, the best way to defend the child against thoughtless barbs of his peer group, if the neighbourhood children know about the problem, is to have discussed his diagnosis with him beforehand.

Attempts have been made to quantitate "death anxiety" in children with fatal illness[6], but the essential issue is not a statistical one. Rather, the central problem of the seriously ill child is emotional — coming to grips, on an individual basis, with death.

Given this fact, one should assume that the most helpful way for adults to meet the emotional needs of the fatally ill child, is to provide an atmosphere in which such children can feel free to express their concerns, one which always provides an honest, complete answer to any question. Once such an environment is established, the physician will quickly realize that most of these children have some knowledge of the seriousness of their illness, that some even know

exactly what is wrong, and that all worry. With this awareness, the doctor can abandon the tact of "protecting" the child, and can thus actively help children cope with the serious concerns which all studies have said exist. The literature shows that such an approach will reduce withdrawal and depression, and hence, be highly gratifying[7].

SUMMARY

We err professionally in adopting a philosophy of not informing patients, including children, about the seriousness of their illness and undercutting talk about dying and death. Surveys indicate that 69-90% of physicians (depending on the individual study) favour not telling, while 77-89% of patients want to know[8]. Our outlook may be too conditioned by the "healthy", rather than the fatally ill themselves.

Not only patients, but most of us, feel less apart when we can share feelings and thoughts about death. Secrecy can keep a child from communicating with his family and friends at a time when he may wish to be closer to them than ever before. This sin of omission can confuse the patient, provoke profound distrust, and even lead to disorganization, for he is not permitted to believe what he consciously and unconsciously knows to be a fact.

We recognize the mental hygienic aspects of being honest in answering questions from children about birth. Clinical perception directs that we do the same for the topic of death. Naturally, how this is done is important. Truth can be cold and cruel, or gentle, merciful, and hopeful. And telling must be suited to the needs and character of the individual child. But the opportunity to discuss feelings helps subdue irrational fears and guilt associated with thoughts of death. A psychological shift occurs, from attempting to repress and forget, to learning to live with the experience.

Our embarrassment at the individual face of death forces the seriously ill child to live alone, with no one to understand him, and the results are too often withdrawal, depression, and occasionally even psychosis. It is wise to remember that the patient with a terminal illness can usually accept what those around him can accept — so whom are we trying to protect?

CONCLUSION

This series of articles has examined the effects which terminal neoplastic disease in children has on the psyche of the patient, his parents, and his physician. Having done so, an approach to the dying child was formulated.

In the process, I hope it has become evident that the prevention of unhealthy psychological reactions to serious illness begins with the diagnosis, and is importantly involved in the interpretation of diagnostic findings and treatment recommendations to the parents and the child.

Thus, in the management of fatally ill children, the doctor can offer help of a supportive nature. In addition, he has the responsibility to act as the integrator of the therapeutic, preventive, rehabilitative, and educational skills of the many medical and para-medical personnel which are available. In so doing, he must draw upon the principles of communication, consultation, collaboration, continuity, and coordination, in order to render such help most effective to the child-patient and his family.

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Janet Markotich, 7T5

Book Review

"THE MEDICINE SHOW"
by the Editors of Consumer Reports.
Consumers' Union, Mt. Vernon, New York
384 pages. Price $3.50

Here is a book which can be heartily recommended for the patient and doctor alike. Aimed at the layman, it is chiefly a no-nonsense guide to coping with the hard-sell tactics of drug companies and the modern-day health fads so widely touted in the popular press. It includes reasonable recommendations on stocking a medicine cabinet, buying prescription drugs and choosing a family doctor.

This book has been prepared by the editors of "Consumer Reports", with whose evaluations of stereo systems and automobiles most of us are already familiar. Although this is primarily an American organization, most of what is said applies equally to the Canadian situation; where there are differences, these are noted by the authors. The premise of the book is that the common everyday health problems facing people today, such as headaches, colds, stomach upsets and the like, can easily be handled, if the afflicted is left to his own devices. However, people are not left alone; indeed, they are overwhelmed by advice on radio and television, the popular press and package labelling. How is one to decide which claims are true and which offer ineffective therapy?

Consumers' Union, using the consultation of a variety of physicians, medical publications (including the Medical Letter), and the U.S. Food and Drug Administration studies and surveys, has analyzed the advertising claims for the common over-the-counter drugs. They compared these results with the product's known effectiveness and came up with many revealing facts.

Among the subjects included are aspirin and its competitors, the common cold, indigestion and antacids, constipation and diarrhea, acne, dandruff, the mouth odour fallacy, female genital deodorants, vitamin E, weight loss, insomnia and anxiety. As each topic is raised, the common misconceptions about treatment are brought out, and studies are quoted to reveal the falsehoods. As well, the over-the-counter drugs are analyzed for content, therapeutic effectiveness and relative cost. Throughout the book, names are named and when a certain brand name product is shown to be no more useful than no drug or a "home remedy", this is clearly stated.

As an example, most over-the-counter cold remedies, while they contain decongestants, antihistamines and analgesics, contain sub-therapeutic doses of all ingredients except ASA. What this amounts to for the consumer is a very high cost for an ASA tablet! Cough syrups which do not contain the only effective cough suppressants sold over the counter (codeine and dextromethorphan) are also shown to contain effective doses of only sugar and alcohol. Some of the popular cough syrups are fifty proof! Ingredients are often insufficient in amount or antagonistic to one another. Advice about antacids is also sensible; chronic use of "candy" antacids containing calcium carbonate is discouraged, and prolonged use of any antacid without a doctor's advice is also frowned upon. The effectiveness and side effects of aluminium and magnesium containing antacids are compared. One popular liquid for digestive upset is shown to contain no antacid at all! Female genital deodorant sprays generally contain an emollient, a perfume and a propellant. These products have been the cause of a very large number of allergic and irritative reactions. Consumers' Union suggests that if a woman has a vaginal odour that is not controlled by simple soap and water, she should see a physician, as there is most likely a pathological cause.

There is a brief but good treatment of many of the "quack cures" for such diseases as arthritis and cancer. The book suggests asking a few critical questions about these "miracles", such as; what is the source of the story? who paid for the study? and what clinical testing procedures were used?

There is good advice on first aid and what to keep in one's medicine cabinet. There are chapters on choosing a family doctor or a hospital – these refer mainly to the American situation which is economically and organizationally quite different from that of Canada, so the Canadian reader will not find them directly applicable. Even so, the basic principles apply to all.

For the consumer of drugs and other "cures" this book has obvious use. It is practical, and is written in an informal, easy to read style with a dash of humour and a lot of good sense. It could well save many people their money and their health.

For the medical student, the book is a gold-mine of information. It offers many practical suggestions with scientific evidence for the management of a multitude of the minor ills his patients will bring him. In addition, there is much product information packed into the volume. The common minor complaints that are virtually ignored in medical school are well treated here, and many of the patients' questions can be answered from a reputable source.

In short, the book makes good reading for all.

(Continued from page 77)

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SPECIAL FEATURE

THE ORIGIN OF THE U OF T MEDICAL JOURNAL 88

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Editorial

With this issue we conclude the 52nd volume of the University of Toronto Medical Journal. This year very encouraging for both the quality and number of "student-authored" papers. Changes in next year's format will be aimed at involving more students in first and second year.

To all those who have worked for the Journal this year, we extend our most sincere appreciation. Interest in the Journal is growing and next year promises to be one of the best ever. Michael Howcroft will be staying on as senior editor and we hope that many of you will find the time to help the publication.

DL
MJH

The Origin of the University of Toronto Medical Journal

Earlier this year it was our good fortune to receive from Dr. Benjamin I. Johnstone (2T4) a short letter on the initiation of the Medical Journal. We would like to share the letter with you.

" . . . After half a century, I thought you might be interested in learning about the birth of this publication. In 1922 Don Campbell of 2T3 was a candidate for presidency of the Medical Society. One of his platform planks was the establishment of an undergraduate Medical Journal. Don was elected president but, for some reason, he did not carry out his plan. The next year – in 1923 – I ran for the presidency and promised to start the Journal, if possible. I was elected president and Jerry Campbell of 2T6 was elected secretary-treasurer.

My first problem was to obtain permission from the faculty. I met with this group consisting of the Dean, Professor Duncan Graham, Professor J. J. R. McLeod, Professor F. W. G. Starr, Professor V. Henderson, and others. They agreed we might go ahead but with two very strict provisos:

1. The word "undergraduate" must be displayed prominently on the front page of the Journal.
2. They would assume no financial responsibility for the undertaking.

Having obtained permission, the next problem was to learn where a Journal could be published. I contacted Mr. Brebner, the registrar, and after some consideration he agreed to publish the Journal provided we were able to guarantee payment.

During the summer of 1923, Jerry Campbell and I visited Eatons, Simpsons, various surgical supply houses, and others whom we thought might be interested in advertising in such a Journal. By the end of the summer, we had obtained sufficient guaranteed advertisements to cover the cost and Mr. Brebner agreed to go ahead with the publication.

Early in the school year, the first issue was published. The executive committee of each of the five years undertook to sell each of their members a copy at ten cents each. The venture did not turn out to be a big money maker but, fortunately, we ended up in the black.

The Medical Society appointed Earle Scarlett, 2T4, as Editor-In-Chief and he selected members from each of the years for his committee. The literary success of the Journal was entirely due to Earle Scarlett and his editorial board . . . "

After 52 consecutive years of publication the Journal remains one of the oldest undergraduate medical publications on the continent.

David Kligman, M.D., C.M.*

Getting the Most out of a Psychiatric Consultation

Knowing how to get the most out of a psychiatric consultation can be difficult for the medical, surgical or pediatric house officer. Psychiatric concepts may seem vague and foreign to the world of heart murmurs, selective angiography and the daily battle with death[1]. It may not even be clear just how much help, and what kind, the psychiatric consultant has to offer. Paradoxically, many medical graduates have had more exposure to the treatment of hospitalized psychotics than to the psychological management of hypochondriasis and the emotional reactions of patients and families to illness and dying. Yet these are everyday problems on an average hospital service.

This paper offers six practical suggestions for the house officer: (I) try to focus the consultation request into a question; (II) organize the data you already have; (III) discuss the case with the psychiatrist; (IV) request consultation early; (V) prepare the patient (and the parents in pediatric cases); and (VI) participate in the interviews if possible (Table 1).

I. TRY TO FOCUS THE CONSULTATION REQUEST INTO A QUESTION

Most requests for psychiatric consultation fall into three groups[2]: (1) *diagnostic* (e.g. "Is this patient's paralysis caused by neurological disease or by conversion?"); (2) *management* (e.g. "How can we get this suspicious patient to take her medications?"); and (3) *therapeutic* (e.g. "Would you take over the primary responsibility for treating this psychotic patient?"). Specifying the nature of the problem and *focusing* it into a question[3] help the consultant to orient himself, assess the urgency of the situation and ask appropriate questions in turn. Even those requests for help that are hard to put into a precise question deserve to be discussed with the psychiatrist. In these cases, the difficulty in pin-pointing the problem can, in itself, provide some information about the patient, who may be giving contradictory messages without knowing it.

II. ORGANIZE YOUR DATA

"We see what we know," a wise teacher of medicine once said. Often, the house officer has a large fund of pertinent information which he cannot use until he has organized and labelled it. By developing the habit of thinking about "problem" patients in the same systematic way each time, the house officer will find himself recognizing recurrent patterns more readily. Each of the following points will be more pertinent to some cases than to others but, as a group, they cover the psychological "clues" that are most frequently of importance.

A. *Detailed description of the consultation problem*

Following from the focused statement of the problem, this should highlight *points of differential diagnostic value* and the *specific circumstances* under which management difficulties occur, when they are the reason for referral. For example, if a patient is behaving strangely, a deterioration at night may be significant, as delirium tends to be aggravated by decreased sensory stimulation[4]. If another patient refuses to obey orders and stay in bed, does he respond differently to various staff members? Which nurse and what approach seem to meet the least resistance?

B. *The patient's medical condition*

This includes *the nature of the illness* (course, chronicity, symptoms and their severity, stage and prognosis) and *medical factors that may affect the patient's mental state*. Among the latter are certain medications, fever, electrolyte disturbances, cerebrovascular insufficiency, hypoxia and hypercapnia. The correct diagnosis of delirium with delusions of persecution was suggested in one case[4] by a review of the medical chart. The patient became febrile on the afternoon of the third post-operative day and psychotic later that evening, accusing the staff of trying to kill him. The diagnosis was confirmed by the presence of fluctuating levels of consciousness and the psychosis subsided, with the fever, in response to medical treatment.

C. *Potential sources of psychological stress.*

The house officer usually knows his patient's recent life history well enough to detect some possible sources of psychological stress. Of course, what *is* stressful for a given patient depends on its personal meaning for him[5, 6] but major life events like becoming a parent, bereavement, marriage, divorce, promotion and failure should be duly noted[7, 8]. Psychological stress may be a precipitant of a wide variety of illnesses[9].

D. *Meaning of the illness to the patient*

Illness may represent a mixture of threat, loss and gain to the patient[10]. He may offer clues about what it means to him in the imagery he uses to describe his symptoms[11] (e.g. a headache that "feels like a hammer pounding on my head"), the way he responds to medical advice[1, 12], and his manner of telling his own medical history[10] and that of his family. An adolescent girl, who discussed her recent operation for an ovarian tumor with little emotion, cried when she described her grandfather's death from cancer of the colon. Apparently, their histories – abdominal pain, distention and several operations – were quite similar. The girl seemed to be expressing some feelings about her own illness in telling about that of her grandfather.

E. *Direct psychological observation of the patient (and family)*

There are several excellent guides to the *mental status* examination[13, 14, 15]. A key factor in the mental status, as in any other examination, is *consistency of method.*

Another source of valuable information is the patient's coping style and manner of relating to staff, other patients and relatives. Seven personality types ("dependent", "orderly", "dramatizing", "long-suffering", "guarded", "superior", "aloof") have been described

*Demonstrator, Department of Psychiatry, University of Toronto.

among medical patients: each requiring a different approach by the doctor[16]. Not infrequently, an understanding of the *doctor-patient relationship* or the *nurse-patient relationship* will unlock difficult management problems. For example, a patient who cannot accept or acknowledge help from the staff may provoke progressively more determined efforts to be of service, followed by increasing frustration with him. Physician and psychiatrist can apply their understanding of the staff's normal reactions and of the patient's special needs to avert or resolve a crisis. Without an individual approach, patients like this sometimes sign out against medical advice.

Family interaction patterns can be equally revealing. What does it tell us when one parent remains aloof from a child patient while the other is involved to the point that all perspective is lost?

III. DISCUSS THE CASE WITH THE PSYCHIATRIST

This is where the collaboration between referring physician and psychiatrist – an essential part of every successful consultation – begins. The referring doctor should count on spending some time discussing the case with the psychiatrist at the outset and again at the conclusion of the consultation[17, 18]. Initially, the discussion may focus on the house officer's concerns and on further defining the consultation problem. The psychiatrist may try to get the physician's *subjective impressions* of the patient. Discussions about the doctor's feelings towards the patient should not be misunderstood as an attempt to "psychoanalyze" the physician. The impressions that people make on us (including how they make us feel) are the raw data of psychiatry. Discussing this material is as pertinent to psychiatric consultation as comparing notes on a heart murmur is to a cardiologic assessment.

The post-evaluation discussion provides an opportunity to work out the details of the recommended approach to the patient. Once again, this is best done by physician and psychiatrist face to face so that questions, doubts and subtleties can be dealt with.

IV. REQUEST CONSULTATION EARLY

Unhappily, it is not altogether rare for a psychiatrist to be called on Friday morning to see a patient who is going to be discharged that afternoon. If he is not called until the neurological examination, neurological consultation, EEG, brain scan, skull X-ray and lumbar puncture all "confirm the absence of organic pathology", he may only have time to bid the patient "Hail and farewell". Needless to say, the psychiatrist bears an equal responsibility to respond promptly to any consultation request.

The view that "physical" illnesses have "physical" causes only, and when one has ruled these out, it is time to call the psychiatrist, is too narrow. It is far more profitable to study the various ways in which *somatic* and *psychological factors interact* in producing illness[5, 19]. There are at least four good reasons for thinking of psychological factors early in the hospital course and requesting psychiatric consultation, when indicated, early:

A. *Anxiety reduction may possibly lead to early discharge.*

In one study[20], reduction of anxiety in a group of pediatric medical patients was associated with early discharge from hospital.

B. *Psychiatric evaluation and planning takes time*

The psychiatrist's work depends on rapport with the patient and, although there are ways of fostering its development[1], sufficient time is required[21]. In a pediatric setting, time must also be allowed for seeing the parents. When a special disposition (e.g. psychiatric hospitalization or discharge to a foster home) is decided upon, time is needed to make the arrangement and, of equal importance, to help the patient and his family begin to work out their feelings about it.

C. *The psychiatrist can make a diagnostic contribution*

Conversion[11], hypochondriasis[12] and the somatic expressions of depression cannot be diagnosed on the basis of exclusion alone. Each must be based on the *presence of specific findings* as well as the absence of others. The diagnosis of somatic complaints in a patient who *is* depressed or who does have an hysterical character can be difficult, to say the least.

A psychiatrist was called to the E.R. to see an elderly man who was complaining of severe abdominal pain. The intern found the patient to be agitated and depressed and noted that his wife had died the previous week. In talking with the man, it seemed that he was indeed mourning his wife but that his description of the pain (which was precise and devoid of imagery) was not consistent with hypochondriasis or somatic delusions.

D. *"Ruling out organic pathology first" can disrupt the doctor-patient relationship*

The hypochondriacal patient has the most to lose by this approach. Often, because his insistence on a physical basis for his distress serves some adaptive purpose, "saying it ain't so" may drive him away[22]. Perhaps the next doctor *will* operate on his abdominal pain. Early psychiatric consultation can help clarify the therapeutic as well as the diagnostic problem, allowing the physician to treat the hypochondriac without unduly threatening his psychological equilibrum. Medical and psychiatric evaluations can proceed together.

V. PREPARE THE PATIENT (AND PARENTS IN PEDIATRICS)

When patients are referred for psychiatric evaluation they may fear that their doctor feels their symptoms (which *are* real and troublesome to them) are "all in their head", "imaginary" or "fake". They also may feel hurt, inferring that the physician must think they are "crazy". This can be dealt with by introducing the psychiatrist as a member of the team, who sees many of the patients when the medical doctors feel it will be of help. There should follow a brief statement of the

doctor's concerns *in terms that are understandable by and acceptable to the patient.*

When patients infer that the psychiatric referral means their symptoms are "all in their head" or that they are "crazy", they should be told the truth: most of the medical and surgical patients seen by the psychiatrist are *not* crazy, and psychological factors play a role in every illness. With adolescents, it is frequently necessary to state this explicitly, even when they don't ask.

One almost universal problem in referring pediatric patients is the guilt aroused in the parents. It is often necessary to counteract the view that Johnnie's problem is a direct reflection of parental failure. Although this may be true in part, the parents' feelings of guilt can be dealt with most effectively bit by bit in a therapeutic situation. If too much guilt is fostered at the time of referral, they will never avail themselves of further treatment.

A ten year old diabetic was referred for evaluation at the request of the mother, who wanted an opinion about his "immature" behaviour. This consisted of tantrums when he did not get his way and an inability to remain separated from his mother for very long. She encouraged this behaviour by giving in to all his demands and by checking up on his whereabouts several times during the interview with her. When asked about this she became extremely guilty and wondered whether she was an "over-protective" mother. She repeated this several times and was obviously relieved when the psychiatrist replied that her son seemed to be asking for that kind of attention and it was very hard for her to say no. The mother subsequently agreed to try therapy for her son and counselling for herself.

Parents may need to know that their child's problem is not a "mental illness" since, in the minds of many. psychiatry, mental illness and involuntary confinement to mental hospital's are closely associated.

VI. PARTICIPATE IN THE INTERVIEWS IF POSSIBLE

Although it requires both the house officer and the psychiatrist to make a special effort to find a mutually convenient time, there is no better way for interns and residents to get the "feel" of interviewing and of the the kind of data on which psychiatrists base their recommendations[1].

In summary, to get the most out of a psychiatric consultation, the house officer should try to focus the reason for the request, organize the facts at his disposal, discuss the case with the psychiatrist, think of psychological aspects of the case and request consultation early, prepare the patient and participate in the interviews. These guidelines can be thought of as goals which the physician will achieve more readily with practice. The psychiatrist is used most effectively when he is seen by the physician and the patient as part of the ward team.

TABLE 1

GETTING THE MOST OUT OF A PSYCHIATRIC CONSULTATION

I. *Try to Focus the Consultation Request into a Question*
- A. Diagnostic
- B. Management
- C. Therapeutic

II. *Organize Your Data*
- A. Detailed description of the consultation problem
  1. differential diagnostic points
  2. management issues
- B. The patient's medical condition
  1. nature of the illness
  2. medical factors that may affect the patient's mental state
- C. Potential sources of psychological stress
- D. Meaning of the illness to the patient
- E. Direct psychological observation of the patient (and family)
  1. elements of the mental status
  2. the patient's coping style and manner of relating
  3. the staff-patient relationship
  4. family interaction patterns

III. *Discuss the Case with the Psychiatrist*
- A. Before the evaluation
- B. After the evaluation

IV. *Request Consultation Early*

V. *Prepare the patient (and parents in pediatrics)*
- A. Deal with parental guilt
- B. Deal with the usual questions patients have
  1. "Do you think I'm crazy?"
  2. "Are you trying to get rid of me?"
  3. "Do you think my symptoms are fake?"
- C. Use the psychiatrist as a member of the team

VI. *Participate in the Interview if possible*

ACKNOWLEDGEMENT

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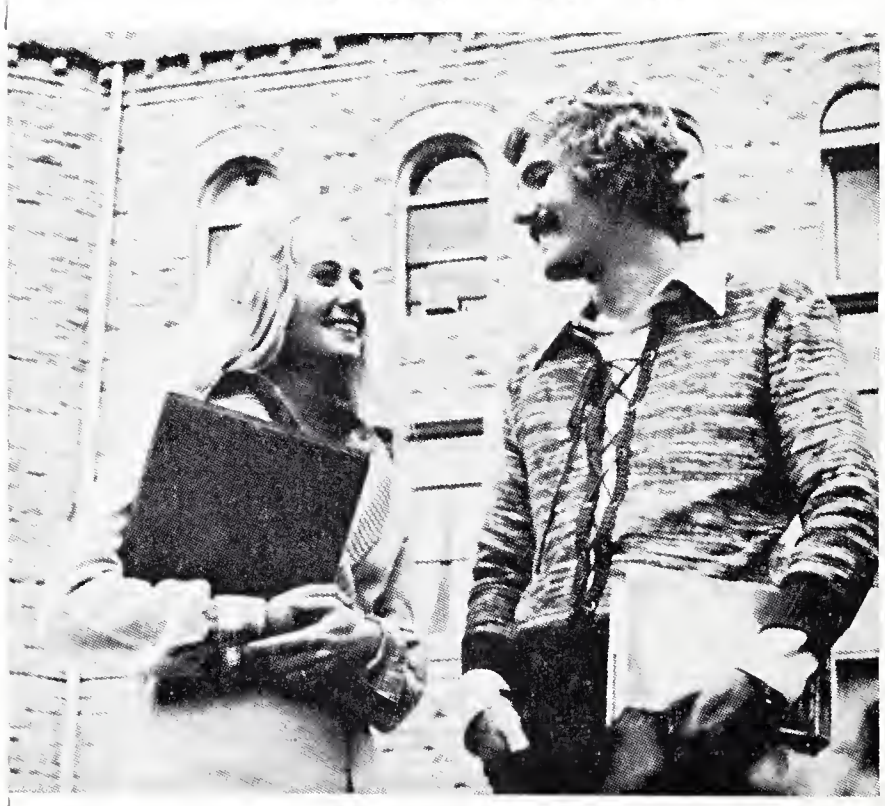

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Prevention of Deep Wound Infection in Total Hip Replacement

M. G. Martin, B.A.Sc., 7T5

INTRODUCTION

Total hip replacements which were performed as early as 1938[1], have become increasingly popular during the past decade. While a total hip replacement may offer a new life to a patient who is virtually chair or bed ridden, deep wound infection, which may present years post-operatively, is a major catastrophe which often necessitates removal of the prosthesis, condemns the patient to chronic pain or infection, or occasionally causes the patient's premature demise. At first, infection rates as high as eleven percent were reported by surgeons whose overall rate in infection was less than one percent[2]. Implicated as causes were the high average age of the patients, the long operating time required, the need for a large wound cavity, and the proximity of the wound to the anus and genitalia. Recent developments have enabled some surgeons to reduce their infection rate to less than one percent. These developments may conveniently be divided into preoperative, intraoperative, and postoperative techniques.

PREOPERATIVE TECHNIQUES

In the assessment of any patient prior to surgery, one must recognize those factors which increase the risk of postoperative infection. General factors such as the person's age, weight, and general health (state of nutrition, use of steroids, chronic illness, etc.) influence the infection rate but are difficult to control. In one series, it was noted that fifty percent of infections occurred in patients whose haemoglobin was less than seventy percent[3], suggesting that anemia should be corrected preoperatively. In a recent review of 1,000 cases, Hunter[4] found an overall infection rate of 2.5%. Of the twenty-five infections, twelve were in hips that had previously been operated on, seven were in patients with rheumatoid arthritis, and four were in patients with an associated infection. These three factors have been associated with high infection rates in several series. Simon et al[5], who reported no infection after sixty-seven procedures, included a careful preoperative assessment for any area of skin irritation or local infection. If either was found, the operation was delayed until the condition could be resolved. Since a direct relationship has been demonstrated between the duration of preoperative hospitalization and the incidence of postoperative infection, these conditions should be treated out of hospital. While investigating the increased infection rate in hips which had undergone previous surgery, Fitzgerald[6] cultured surgical specimens from 688 hips and obtained positive cultures in 11 of 437 "new hips" and in 84 of 221 "old hips". There were seven postoperative deep infections, and it was noted that in some cases the responsible organism was not identical to the one cultured at operation.

Two additional factors, the use of prophylactic antibiotics and meticulous skin preparation, are also recognized as important considerations for preventing infection. The use of prophylactic antibiotics remained controversial for almost two decades but most authors now agree on their effectiveness when begun preoperatively. Ericson[7] reported infections in twelve out of eighty-one patients given cloxacillin preoperatively. Simon[5] recommends preoperative intravenous cephalosporin in combination with intramuscular gentamicin starting the evening before surgery. Patients with cephalosporin allergy may be given intravenous lincomycin. While no particular schedule of prophylactic antibiotics has been shown to be superior, their use should be governed by two simple rules: 1) The antibiotic should be bactericidal against the common organisms involved (in most cases this is *Staph. aureus*). 2) The drug should be given preoperatively to ensure high tissue levels at the time of surgery.

As with prophylactic antibiotics, no program of skin preparation has been proven superior, but most authors agree that skin sterility is increased with each scrub and that at least two scrubs should be done in the 24 hours before the patient arrives at the O.R.

INTRAOPERATIVE TECHNIQUES

While pre and postoperative factors have permitted a significant reduction in the rate of infection, intraoperative methods of prophylaxis remain the most crucial and the most contraversial. Charnley[8], a pioneer in this field, outlines four sources of surgical wound infection: airborne organisms, skin borne organisms, blood borne organisms and organisms on the surgeon's gown and gloves. These four factors are each enhanced by the length of the operating time and the size of the hematoma.

Prophylaxis against contamination with skin and blood borne organisms begins preoperatively with proper skin preparation and with prophylactic antibiotics. In the O.R., the skin should be prepared by diligent scrubbing with agents such as "Betadine". Disposable drapes are then used with clear plastic adhesive draping, sealing off both the operative site and the perineum. The antibiotic selected preoperatively is added to an intravenous solution and administered throughout the procedure.

Attempts to eliminate airborne organisms have led to the concept of the "clean air" O.R. Achievement of such an atmosphere is based on three principles: the killing of airborne bacteria, elimination of bacterial sources, and the removal of bacteria by continuous filtering of O.R. air. Experiments with ultraviolet light as a method of killing airborne bacteria demonstrated that ultraviolet light could lower the number of viable bacteria by more than 95%; however, the technique has not proved to be an effective method of preventing infection. By contrast, removal of bacteria by continuous filtering of O.R. air has been promoted as a highly effective technique of preventing surgical infection. Charnley[9] reported that the addition of a laminar flow, clean air system to his operating room reduced his infection rate from 8.9% to 1.3%. Auspach[10] sampled

the air directly over the wound site and found that the use of air filters reduced the density of airborne particles from 70,000/m.^{3} to 220/m.^{3} It has also been shown that the number of viable bacteria are substantially reduced by this technique and that any movements or conversation in the operating room is accompanied by an increase in the airborne bacteria. For this reason it has been recommended that the operating room be sealed off and conversation kept to a minimum once the procedure has begun. Several "personnel barrier" systems have been designed which attempt to further isolate the operator from the patient. These have included the use of visored hoods and bubble helmets. Recent attention has also focused on possible sources of bacteria in the O.R., incriminating such areas as the anaesthetic machine, the storage shelves, and the lighting fixtures.

Charnley's fourth potential source of contamination was direct spread from organisms on the surgeon's gloves and gown. Cultures taken from surgeon's gloves pre and postoperatively have shown that this may indeed be a source of wound contamination and methods of controlling this include the use of disposable gowns, air-conditioning to minimize perspiration, and "double-gloving".

While the preceeding discussion centres around methods of preventing bacteria from reaching the wound, irrigation with topical antibiotics further reduces the infection rate, not only by its direct bactericidal action, but also by removing clots and devitalized tissue. Schen[11] was able to reduce his postoperative infection rate from 2.5% to less than 1% by adding a mixture of bacitracin and polymyxin B to the normal saline irrigation solution he had been using.

As was mentioned, operating time and hematoma size are also determinants of the infection rate and these should be minimized through careful operative technique. Use of a pressure dressing and hemovac drain in the immediate postoperative period help to decrease hematoma size.

POSTOPERATIVE

Little has been written about postoperative factors which contribute to wound infection. As mentioned, proper dressing and drainage prevent the formation of an excessive hematoma and everyone involved in wound care should observe flawless sterile technique; for example, one must remember that attempts to express a hematoma may suck contaminated fluid back into the wound.

The antibiotic started preoperatively should be continued for ten days to two weeks postoperatively. Some surgeons recommend continuing the antibiotic prophylactically for dental and urological procedures in the one to two year period postoperatively.

DISCUSSION

The prophylactic techniques discussed in this paper are summarized in Table 1. While these technique have contributed to a significant reduction of the infection rate, a zero rate necessarily depends on the strict adherence to good aseptic operative and postoperative technique by all personnel.

TABLE 1: SUMMARY OF FACTORS IN PROMOTING ASEPSIS

(1) *Preoperative*
- Patient Selection and Preparation
- Intravenous Antibiotics
- Skin Preparation

(2) *Intraoperative*
- Skin Preparation and Draping
- Clean Air Room
- Strict Asepsis by Staff including use of Special Gowns, Caps and Gloves
- Wound Irrigation
- Bactericidal Antibiotics
- Minimal Operating Time

(3) *Postoperative*
- Pressure Dressing
- Hemovac Drainage
- Bactericidal Antibiotics

While deep wound infection remains an important cause of failure in total hip replacement, its prevalence has been significantly reduced through modern aseptic techniques. Many infections are "late" infections, presenting months or years postoperatively. For this reason, it is difficult to know whether their appearance has been prevented or delayed. While it has been shown that the incidence of late wound infection parallels that of early infection, the mechanisms of late infection are not yet fully understood. The persistence of late infections with a continuing decline in the incidence of early infection may emphasize the need for long term prophylaxis or modifications of the presently used prostheses.

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*Hexachlorophene Toxicity in the Dog**

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INTRODUCTION

Only recently has it been realized that hexachlorophene, which has for many years been a popular and widely used antibacterial agent, is extremely toxic and can pose a potential danger if not properly used. Now preparations containing hexachlorophene in a significant concentration come under federal government control and are available only on prescription.

CLINICAL CASE

The senior author was asked to consult to a novice dog breeder who had a litter of eight two-week old Great Dane pups, all of whom were exhibiting similar nervous signs of shaking and incoordination. Examination of the animals revealed that the pups were otherwise nursing and healthy, the mother was in good health and she had had an uneventful delivery. The diet appeared to be adequate and the pups were being supplementally fed by bottle, which is a usual procedure with a large litter.

Careful questioning of the breeder suggested two possible causes for the nervous signs in the pups. Being concerned about cleanliness, the breeder had been spraying the newspaper bedding for the pups, each time it was changed, with a popular commercial aerosol disinfectant spray. This spray contained phenol which can be extremely toxic for animals. The other more likely cause of the problem appeared to be a commercial antiseptic lotion which had been designed by the manufacturer for application to the backsides of human bed patients to prevent bedsores. This lotion had been applied twice a day since the pups were one week of age, to the mammary glands of the mother dog, to heal any scratches or bites from the suckling pups. Thus the pups had obviously been ingesting the lotion when sucking. The lotion contained hexachlorophene, sodium borax and methylparaben – any of which could conceivably have been causing the nervous signs. Upon recommendation, both the procedures of spraying the newspapers and applying the lotion to the mammary glands of the mother dog were immediately stopped.

To summarize, the breeder had started applying the lotion to the female dog's mammary glands when the pups were one week of age. Nervous signs were noted by the breeder in the pups by thirteen days of age. The lotion was discontinued, upon recommendation, at sixteen days of age.

Because of the financial value of the puppies, none of the animals were available for necropsy and examination. By six weeks of age all the pups in the litter had shown complete clinical recovery and appeared normal. We felt that it was important to determine if the commercial lotion was in fact the cause of the nervous signs, and if so, what ingredient in the lotion was toxic.

EXPERIMENTAL STUDIES

Materials and Methods

One-week-old mongrel puppies were dosed orally twice a day with 0.1 ml of the lotion that the dog breeder had been applying to the mammary glands of the nursing female. These puppies were observed for development of clinical signs similar to the Great Dane puppies.

With the cooperation of the manufacturer, a synthetic duplication of the original lotion was prepared. In addition, a series of synthetic duplications were prepared with each preparation in the series lacking a different ingredient from the formula of the original lotion. These ingredients included hexachlorophene, methylparaben and sodium borax. One preparation was prepared minus all three ingredients to rule out the possibility of materials incorporated into the formulation as carriers, causing the syndrome. A total of two pups were dosed with each preparation. Three non-treated littermates served as controls. All pups were observed for a period of seven days for the development of neurological signs.

At the end of the period of observation, all pups were euthanized with an overdose of sodium pentobarbitol. Tissues examined histologically included brain, spinal cord, sciatic nerve, heart, liver, kidney and spleen.

Results

Clinical signs identical to those exhibited in the Great Dane pups developed in the mongrel pups dosed with the original lotion obtained from the breeder. Signs typical of those seen in the original cases were seen in the pups within a week after the dosing was started.

Clinical signs also developed in pups which received the complete synthetic preparation, the synthetic preparation minus sodium borax and the synthetic preparation minus methylparaben. It was therefore concluded that hexachlorophene was the toxic agent (See Table 1).

Histological examination of brain tissues confirmed the above, with marked vacuolization of white matter, especially in the brain stem region, being observed only in dosed puppies that had exhibited neurological signs.

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* Synopsis of a paper presented at the 111th Annual Meeting of the American Veterinary Medical Association, Denver, Colorado, July 1974 and to be published in the Journal of the American Veterinary Medical Association.

TABLE 1
HEXACHLOROPHENE TOXICITY IN NEONATAL PUPPIES

Puppies dosed with:	Clinical Signs of Ataxia and Tremors	Histological Lesions of Brain White Matter
Original Lotion	Yes	Yes
Synthetic Preparation Complete	Yes	Yes
Synthetic Preparation Minus Borax	Yes	Yes
Synthetic Preparation Minus Hexachlorophene	No	No
Synthetic Preparation Minus Methylparaben	Yes	Yes
Synthetic Preparation Minus Borax, Methylparaben and Hexachlorophene	No	No
Undosed Controls	No	No

These histological lesions were of similar magnitude in all the affected groups. There was marked vacuolization of the white matter of the medulla oblongata and the metencephalon with extension into the mesencephalon. There was little detectable histological difference in the cerebral region of all the groups examined histologically. In summary, lesions were confined to the brain stem region and consisted of a massive vacuolization of the white matter with apparent absolute sparing of the grey matter including the cerebellar cortex and nuclei of the prosencephalon and brain stem region. Vacuolization of white matter extended throughout the arbor vitae into the cores of the cerebellar folia and extended to many areas of the pons and medulla oblongata and throughout the spinal cord (see Figures 1-3). The neurological deficits observed clinically in the affected animals were attributed to the leukoencephalopathy herein described.

EXPERIMENTAL HEXACHLOROPHENE TOXICITY STUDIES IN PUPPIES

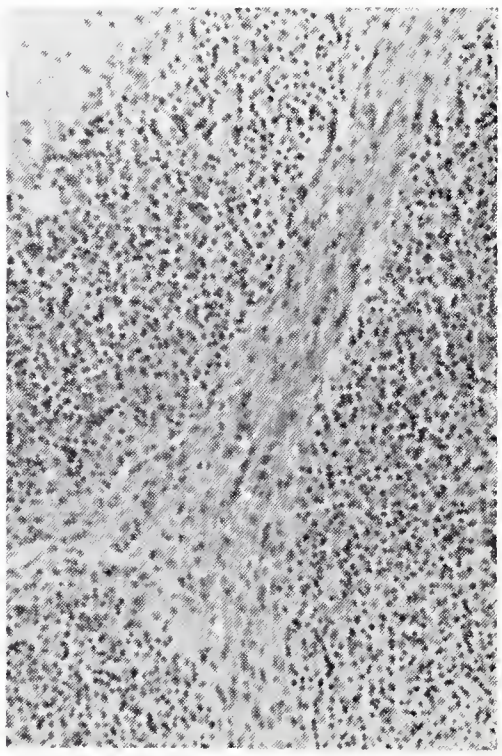

FIGURE 1: Section of cerebellum from control pup showing internal granular layer and white matter (centre).

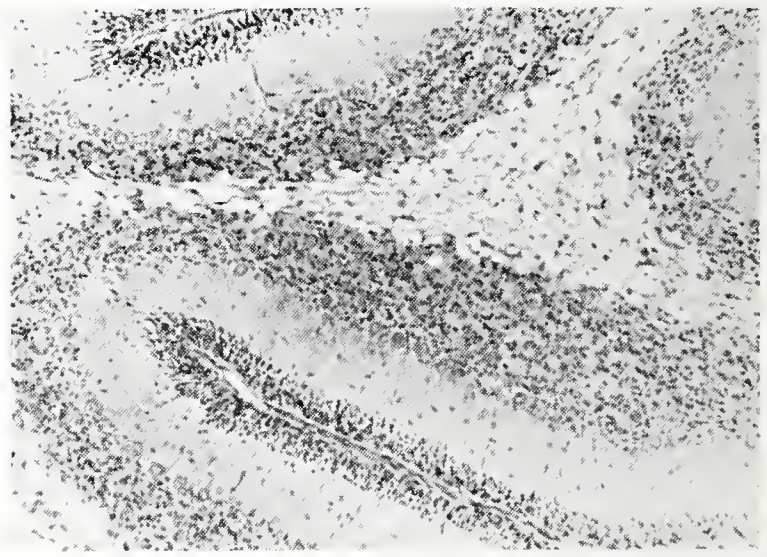

FIGURE 2: Cerebellum from pup treated with hexachlorophene-containing lotion. Note the extensive moth-eaten appearance of the cerebellar white matter.
H. & E., X 150

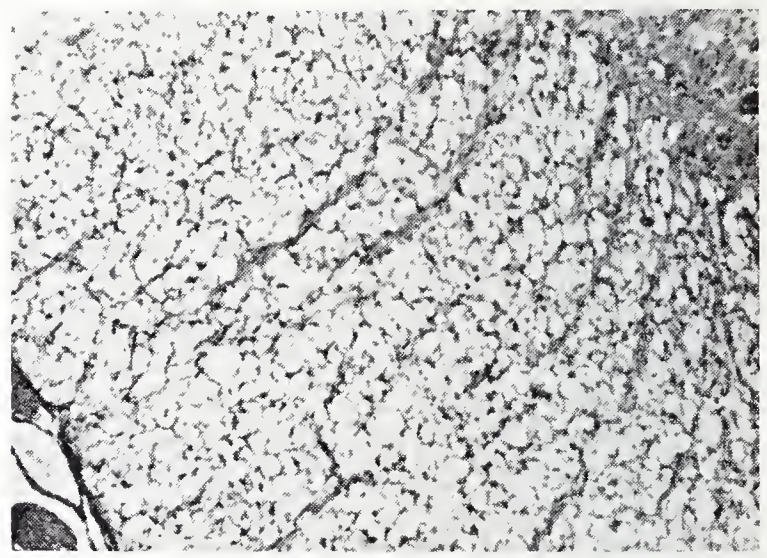

FIGURE 3: Cervical area, spinal cord from puppy treated with hexachlorophene lotion. There is marked vacuolation of all funiculi. Note the sparing of the grey columns (upper right), and spinal nerves (lower left).
H. & E., X 375

DISCUSSION

A review of experimental studies in animals, as relating to toxicity of hexachlorophene in man, refers to studies in dogs.[3] A comprehensive review of the problem in man with reference to history, experimental studies and legislation is given in a series of papers presented at the Annual Meeting of the American College of Clinical Pharmacology.[1, 4, 6, 9]

Recent reports have appeared in the veterinary literature concerned with hexachlorophene toxicity in the canine species. Attempts to produce clinical signs of toxicity using hexachlorophene soap and hexachlorophene powder orally, succeeded only when a level of 450 mg of hexochlorophene powder was given to adult

dogs in a single dose.[7] This resulted in death. Nervous signs have been described in three-week-old pups dosed with hexachlorophene.[2] A dose of 7.5 mg/kg of body weight was required, however, to cause significant clinical signs with gross and histological lesions. These lesions were described as edema and extensive vacuolization of the white matter of the cerebrum, cerebellum and spinal cord.

The clinical case described here is of interest to the veterinary clinician as special circumstances permitted accidental poisoning of a litter of Great Dane puppies. Defining the cause was important to the dog breeder involved, both financially and in respect to any future breeding programme. As the puppies recovered, they could be sold for breeding purposes without concern for propagating a possible inherited neurological defect. In addition, test-matings were not required to eliminate the possibility of hereditary defect.

The clinical case is of medical importance as it adds even more support to the recently acquired and unquestionable data that has proven hexachlorophene a dangerous substance that society must learn to use with more respect than it did in the past.

Up until recently, it had been a long standing practice in many hospitals to bathe newborn infants with 3% hexachlorophene preparations in order to reduce staphylococcal infections. The sodium salt of pentachlorophenol has been used in the laundering of nursery linens in hospitals. Trichlorocarbanilide, often used in diaper washes, can break down during autoclaving to result in aniline which is toxic. Hexachlorophene, incorporated into hand and bath soap, is absorbed through the intact skin in adults. Studies have shown that females absorb twice as much hexachlorophene by this route than males.[6] Hexachlorophene used in surgical scrub preparations results in similar absorption through the skin.

Recently, a correlation was made between lesions in infant brain stem sections on file in the Pathology Department at the University of Washington, and hospital records of hexachlorophene baths being given to infants at the Children's Orthopedic Hospital and the University Hospital.[8] Out of a total of 250 brains examined, 21 showed vacuolization in the reticular formation and various long tracts. All but two of the twenty-one cases involved had received three or more documented total body baths with 3% hexachlorophene. Brain sections from infants who had not been bathed in hexachlorophene did not have vacuolated lesions.

In France, during 1972, an unusual combination of dermatologic and neurologic symptoms appeared in infants, which was subsequently associated with the use of a certain talcum powder.[6] This talcum powder was later found to have been contaminated with 6% hexachlorophene. Several babies died. It is speculated that hexachlorophene was mistakenly added to one or more batches of the talcum powder by the manufacturer.

It is felt that "burn encephalopathy", characterized by convulsions in burned patients, is associated with the application of hexachlorophene to large areas of burned skin to control secondary bacterial infection.[5]

This kind of data, much of it accumulated in retrospect, should lead one to strongly support the control of formulations containing significant amounts of hexachlorophene. This should include regulation of over the counter sales and formulations available only by prescription.

SUMMARY

Ataxia and tremors, affecting the entire body, were seen in all eight pups from a litter of two-week-old Great Danes. They were healthy in all other respects. Investigation incriminated a commercial lotion preparation containing 0.5% hexachlorophene, designed to be used as an antiseptic lotion on hospital bed patients. The dog breeder had been applying this lotion twice a day to the mammary glands of the female dog, since one week post-partum, in an attempt to heal abrasions caused by the nursing pups.

Experimental studies were performed in mongrel pups and showed that the commercial lotion was in fact the cause of the neurological signs in the Great Dane puppies. Further studies were performed to determine what ingredient in the commercial lotion was the toxic factor. This was determined to be hexachlorophene.

Histological examination of the central nervous system of the experimental animals showed marked vacuolization of white matter throughout the central nervous system and spinal cord.

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Viewpoint on Medical Ethics

Stephen G. Fowler, B.Sc., 7T6

" . . . science contains nothing that does not come through the senses. The spiritual world, the nobler side of man's being, has been rejected altogether, banned as it were triumphantly, perhaps even with hatred. The world has proclaimed freedom, now more loudly than ever; but what do we find in that freedom of theirs? Nothing but enslavement and suicide! The world says: "You have as much right as the rich and the mighty. Don't hesitate to satisfy your needs; indeed, expand your needs and demand more." This is the worldly doctrine of today, and they believe that this is freedom. The result for the rich is isolation and suicide, for the poor, envy and murder."

The Elder Zosima
in Dostoevsky's
The Brothers Karamazov

Although the above passage was written in the 19th century, it is regrettable that evidence of its current relevance is everywhere one wishes to look, both within and without the sphere of medicine. Apparently the elevation of self to the centre of one's world ultimately leads to the breakdown of relationships, to the coldness of isolation, in effect, to death.

For centuries, societies have invested their trust in the persons whom they have designated as physicians, in the understanding that these individuals would do their utmost to care for the deepest as well as the more superficial personal needs of societies' citizens. Traditionally, the character of the 'doctor-patient relationship' has been one of trust, respect, understanding – that rare environment in which personal self-disclosure is safely acceptable. Unfortunately, recent public opinion indicates quite clearly that the patient is less than satisfied with the quality of interpersonal relationship he is experiencing with his physician.[1] Most patients are disappointed to find that they are as isolated from their doctor as they are from most other persons within their social sphere. Surely it is disturbing to a doctor, whose profession is to maintain the personal and physical integrity of the individual, to be made to understand that his impact on patients is more a shattering of personal dignity than a bolstering thereof.[2] One hears constantly of disgruntled individuals who are saying that physicians are not what they used to be. Every naive medical student can recall instances when the clinician has callously overlooked the patient in preference for his electrolytes or his 'schizophrenic' symptomatology. Notwithstanding all the inadequacies inherent in any health care delivery system including our own, there must be some basic reasons for the variable degree of isolation that every individual experiences in modern society generally, and specifically in contact with the medical world. I believe that some basic presuppositions in the thinking of the western world account for this general feeling of isolation, for the erosion of the public's confidence in medical doctors, and for some of the dilemmas we are encountering in medical ethics.

Recourse is inevitably made in any discussion of medical ethics to the Hippocractic Oath, whose principles have provided the core for subsequent revisions. Although Hippocrates' appeal was to the ancient Greek gods, the ideals of the oath were sufficiently akin to the principles of physician conduct derived from the Judeo-Christian tradition, that the western world's code of ethics, while claiming the authority of the God of the Bible, incorporated the noble principles of the earlier code. For centuries this code has been the basis for common agreement among most members of the profession and has served to provide the public with some guarantee that standards of physician conduct would be maintained. But underlying the ethics of the 'Christian' world has been the fundamental concept of the 'sanctity of life', governing even the formulation of law by western societies.

The present century has seen the erosion of this traditional structure, largely because of the abandonment of any true appeal to an absolute deity, and the widespread adoption of existentialist philosophy of evolutionism. In a world 'come of age' as modern theologians are wont to say, no longer is there any need to have recourse to God – we can explain our universe and function satisfactorily on the basis of scientific discovery and determinism. Life is obviously no longer sacred in such a system. It can take on value only as each individual sees fit to ascribe value to it. On a broader scale, responsibility now rests with society to establish by general agreement (in actual practice, the agreement of the majority) what value is to be placed on human life and what standards of conduct shall be acceptable. No longer is there any divine, final authority on which to base moral decisions.

Now it is evident that in order to determine the value of life or a behaviour (whether right or wrong) there has to be a universal standard for lesser standards to have any meaning. "Without it there is no final answer to the questions, 'Why should I?' or 'Why shouldn't I?' "[3] Because medicine is a scientific discipline, "Medical opinion is confused and cannot help in the matter of standards".[3] Having disregarded divine revelation, the only practical solution is to uphold as an ultimate standard the criterion of 'usefulness in the achievement of happiness as an end in itself'. Glanville Williams states that, "as an ethical theory (utilitarianism) depends upon an intuited premise, namely that the greatest happiness of the greatest number of human beings is the supreme good. This intuited premise or categorical imperative may be given any one of a number of interpretations, according to the opinion of the particular moralist who puts it forward."[4] Consequently, who is to judge Hitler's Nazi regime for destroying numerous lives in the high name of scientific experimentation? Why shouldn't one race, a majority, decide to exterminate another on the basis of an arbitrary or substantiated decision that the former would profit from the latter's demise? Why should we not determine that the unborn, nascent human life shall be deprived of 'human rights' at the capricious wishes of a few individuals whose concern is to avoid suffering or inconvenience? Why shouldn't an individual gratify his own desires at the expense of the long-term well-being

of his neighbour? A hedonistic world-view such as the Elder Zosima described does not admit the concept of responsibility; suffering is devoid of meaning in a moral system which disregards God and any intrinsic value in one's fellow.

With all due respect to the humanist's approach to the individual, ultimately the metaphysical foundation for such activity is at best obscure, and cannot in the final analysis ascribe any eternal value or meaning to human existence. Having again laid aside the spiritual aspect of man's being, humanism presupposes that the individual possesses limitless insightful wisdom regarding what is good for another, irrespective of the former's own emotional restrictions and personal deficiencies.

Doctors are by no means immune to their philosophical and moral environment; in fact, it has become incumbent upon the physician to act as arbiter in many of the moral disputes of our day. As elsewhere, consumerism has invaded the practice of medicine, bringing more and more demands upon the technical know-how and time of the physician, while at the same time increasingly failing to provide him with the equipment essential for dealing with real human problems. Why is there such little time allotted within the medical school curriculum for dealing with medical ethics? If there are no ready answers, at least students should be stimulated to contemplate the basis upon which they will formulate decisions (because decisions will inevitably be made). How many students/physicians have either the inclination or the time to research their own view of man and themselves, a view which whether ill or well-considered, will become their modus operandi in dealing with patients who will be influenced by their encounter with their physician. To simply adopt the prevailing outlook of our current society may be to court 'isolation and suicide, envy and murder'. Particularly in the practice of medicine, values cannot be divorced from facts. As E. H. Carr wrote in "What is History":

> "When we want to know the facts, the questions are prompted by our system of values. Our picture of the facts of our environment is moulded by our values, i.e., by the categories through which we approach the facts; and this picture is one of the important facts of which we have to take into account. Values enter into the facts and are an essential part of them."[5]

EPILOGUE:

My personal view of the doctor-patient relationship has been markedly enriched by the recognition, under Biblical authority and revelation, of each life, no matter how obscure, as a living entity, possessing meaning and eternal worth, inhabiting a world system in which personal suffering can be meaningful. On the other hand, the despair we are confronting in personal lives, in ethical dilemmas, indeed in the world at large, is attributable to mankind's spiritual depravity.

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David E. C. Cole, 7T5

Inherited Disorders of Amino Acid Metabolism

INTRODUCTION

It is now 70 years since Garrod first proposed that a single defect in a chain of metabolic reactions might be responsible for the manifestations of clinically defined syndromes, and correctly identified three aminoacidopathies – cystinuria, alcaptonuria and albinism. And it is 25 years since Bickell described the effectiveness of restrictive dietary therapy for phenylketonuria (PKU).

The identification of discrete defects of amino acid metabolism has increased exponentially with time. There are now more than 80 disorders known – some benign, some uniformly fatal, and a number with reversible morbidity.

With the recent advances in preventive therapy, there is greater incentive to involve the primary physician in programs for detection and continuing care. When an amino acid disorder is suspected, diagnostic work-up is performed and a therapeutic protocol may be established by the metabolic specialist in a regional centre. The practitioner is then encouraged to familiarize himself with the literature and to make periodic consultations with the specialist so that he can confidently and knowledgeably supervise treatment and provide good followup care. This trend, and the need for mass screening, makes inherited amino acid disorders a relevant subject for general practitioner and specialist alike.

Is it worth the effort? Three factors must be considered: 1) frequency of occurrence, 2) clinical morbidity and efficacy of preventive measures, and 3) availability, cost and accuracy of tests for detection and diagnosis[1].

INCIDENCE AND SIGNIFICANCE – AN OVERVIEW

Phenylketonuria is the prototype of amino acid disorders. Inherited as an autosomal recessive genetic deficiency of phenylalanine hydroxylation, it occurs in approximately 1 in 11,000 live births, and is detectable by screening and treatable by restriction of phenylalanine from the diet. Since the initiation of mass screening and subsequent early detection of affected infants, the classical presentation of PKU – the 6 year old child with severe and irreversible mental retardatoin, eczema and convulsions – is now a rare entity[2]. There are other less frequently occurring aminoacidopathies with similarly tragic results when left untreated (Table I). Inherited as recessive traits, they are clinically undetectable in the parents and therefore can be diagnosed only by mass screening, before signs appear in the homozygous child.

TABLE I: Frequency and Signficance of some Inheritable Amino Acid Disorders

Significance		*Frequency* >1/20,000	1/20,000 → 1/200,000	<1/200,000
Of Immediate Clinical Significance	Neonatal Manifestations	—	hereditary tyrosinemia branched chain ketoacidosis arginosuccinic aciduria hyperglycinemia	
	Insidious Onset	phenylketonuria malignant hyperphenylalaninemia	homocystinuria	—
Of Delayed Significance		cystinuria	—	Fanconi syndrome
Benign		benign hyperphenylalaninemia ?histidinemia iminoglycinemia Hartnup disease	cystathioninuria	—

For example, defective oxidative metabolism of branched-chain amino acids results in branched-chain ketoacidosis or maple syrup urine disease, which manifests as vomiting, hypertonicity progressing to loss of reflexes, convulsions and death in the neonatal period[3]. However, with the early implementation of a semisynthetic diet restricting branched-chain amino acids, normal physical and mental growth has resulted[2]. A mass screening program has a critical role in improving the prognosis for the affected infant.

There is, as well, a group of disorders that appears to be treatable by very large supplementations of essential enzyme co-factors or their precursors. Because a substantial proportion of patients with these disorders respond to co-factor administration, they have been termed the 'vitamin-responsive aminoacidopathies'.[2] Administration of thiamine (B_1) in some infants with maple syrup urine disease, pyridoxine (B_6) in those with cystathioninuria and some homocystinurics, and cyanocobalamin (B_{12}) in methylmalonicaciduria[3] are examples of effective and simple treatment regimens established on the basis of an understanding of the metabolic derangements consequent to enzyme deficiency.

Yet another group of disorders is characterized by delay of manifestations until later childhood or adulthood. Cystinuria, occurring in 1 in 8,000 individuals, is the most frequently seen. The defect is one of impaired dibasic amino acid transport across renal and sometimes

intestinal epithelial membranes. Clinical symptoms occur when concentrations of cystine in the urine are high enough to cause formation of stones. Effective treatment with increased fluid intake, alkalinization of the urine by bicarbonate or citrate and oral administration of D-penicillamine (which forms a cysteine-penicillamine conjugate more soluble than the cysteine-cysteine or cystine conjugate) is possible with many of these patients, and can be improved by early diagnosis and prophylactic follow-up.

CLINICAL DIAGNOSIS AND MANAGEMENT IN THE NEWBORN

Where screening is not available, early clinical diagnosis of the acute onset disorders is essential. Because signs of metabolic dysfunction are non-specific, a careful history is invaluable. Enquiries should be made with regard to:

1) family history: parental consanguinity or previous siblings with similar problems.
2) onset of signs: amino acid disorders manifest after the first few protein feedings.
3) unusual odours: maple syrup odour (branched-chain ketoacidosis) or 'sweaty socks' odour (isovaleric acidemia) about the infant may be diagnostic.

Signs of amino acid disorders are confined chiefly to the neurological and gastrointestinal systems. The onset of failure to feed and vomiting or lethargy, convulsions and altered reflexes (progressing to coma in some) are often attributable to more common problems such as sepsis, central nervous system disease or fluid-electrolyte disturbances. However, inborn errors of metabolism, including amino acid and carbohydrate metabolic disorders, must be considered concurrently.

TABLE II: Laboratory Investigation Indicated when Aminoacidopathy is suspected in Newborn

Serum/Blood	– routine electrolytes
	– gases
	– calcium
	– magnesium
	– bilirubin
	– sugar
	– ketones
	– ammonia
Urine	– reducing substances
	– bilirubin, urobilin
	– ketones
	– ferric chloride test (for PKU and other specific reducing substances)*
	– DNPH test (for ketoacids)*
	– nitroprusside test (for sulfhydryl groups)*
	– nitrosonaphthyl test (for tyrosine)*

* these may be considered as qualitative tests, preliminary to quantitative analysis for the specific amino acid disorders.

Laboratory investigations should include appropriate samples for culture and sensitivity. Blood and urine should be obtained for chemistries as outlined in Table II. Ammonia and ketone estimations are particularly important. Ketosis in the newborn is most often a manifestation of inborn metabolic disorder, and is not commonly associated with a lack of carbohydrate supply as found in those past the neonatal period. Similarly an elevated blood ammonia in the absence of detectable liver disease is almost invariably secondary to amino acid disorders. Either of these findings in conjunction with evidence of hypoglycemia and metabolic acidosis with compensatory respiratory alkalosis provides a high index of suspicion. The ferric chloride test and the 2, 4-dinitrophenylhydrazine (DNPH), nitroprusside and nitrosonaphthyl tests, if available, may lead to a more specific diagnosis[4]. Where there is reason to suspect aminoacidopathy, a trial of protein restriction and vitamin supplementation is warranted until more definitive studies can be carried out[2].

EARLY DETECTION BY MASS SCREENING

Screening may be defined as an effort to detect individuals with genetic defects in the general population or in segments of the population irrespective of recognizable clinical manifestations of that defect. The accuracy of a screening test is contingent upon two aspects – sensitivity (incidence of false negatives) and specificity (incidence of false positives). With genetic diseases, sensitivity is essential, although substantial non-specificity makes further studies costly and cumbersome. The initial impetus for mass screening was stimulated in 1961 by Robert Guthrie's development of the bacterial inhibition assay (Fig. 1) – a technique which is quite sensitive, reasonably specific and which can be quickly and easily carried out as a semi-automated procedure in centralized laboratory facilities on specimens collected from outlying regions[5].

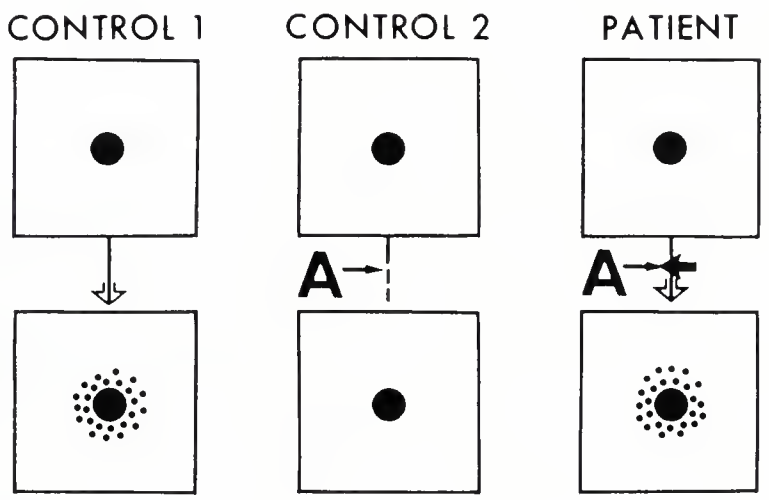

Figure 1. Principles of the Bacterial Inhibition Assay[5]
I) An amino acid-requiring bacterium is supplied with appropriate medium for replication.
II) Addition of an analogue with competitive inhibitory properties prevents colony formation.
III) Addition of urine or serum from the affected patient provides sufficient amino acid to overcome inhibition by the analogue.
(specific reactants for the PKU assay are indicated in parentheses).

By 1969, all of the Canadian provinces except Newfoundland were conducting mass neonatal screening programs for PKU[6]. Soon after, it became feasible to

screen for different disorders simultaneously by one-dimensional paper chromatography of blood and urine samples. These two methods now form the basis of detection by mass screening. Two programs – one in Massachusetts and one in Quebec – have been extensively broadened to include other inherited disorders. The Quebec genetic program now screens for a number of metabolic defects, inculding branded-chain ketoaciduria and hereditary tyrosinemia (relatively more frequent among those with French-Canadian ancestry) by chromatography. Compliance is an acceptable 92% and higher[6].

In 1972 the Massachusetts program identified 35 newborns with abnormal amino acid metabolism among the 80,000 screened – an incidence of 1 in 2,500[7]. This compares quite favorably, for instance, with the detection rate of one previously unsuspected *in situ* carcinoma of the cervix for every 1500 Papanicolaou smears performed[8]. Furthermore, a cost-benefit analysis reveals that a substantial economic return in terms of decreased need for long-term institutionalization is possible. An estimated $300,000 (45% of costs) was saved in that period as a result of early identification and treatment. With more efficient screening procedures and the introduction of more advanced techniques such as amniocentesis, improvement of detection is likely. While figures are not yet available for the Quebec program, similar social and economic factors imply that substantial benefits in medical and economic terms are possible here in Canada as well.

SUMMARY

Increased understanding of inherited amino acid disorders and their treatment, accompanied by more comprehensive and accurate screening programs, will not only benefit those few unfortunate individuals born with these disorders, but will also help relieve the financial and social burden that a society committed to optimal health care must continually bear.

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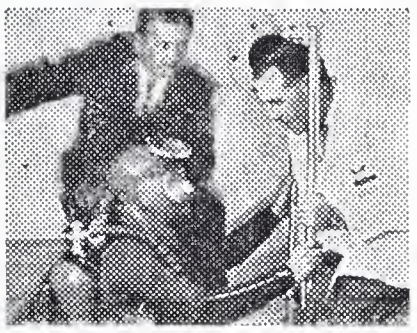

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